Near-Infrared Spectroscopic Diagnosis of Acute Compartment Syndrome

Matthew J Hope

BSc(MedSci), MBChB University of Edinburgh,

FRCS(Tr and Orth)

A thesis presented for the degree of Doctor of Medicine (MD)

at the University of Edinburgh

2008

ABSTRACT

Introduction: Near-infrared Spectroscopy (NIRS) is a technique that can non-invasively determine the oxygen saturation of haemoglobin in the tissues (StO_2) by the differing absorbance patterns of the deoxygenated and oxygenated molecules. An acute compartment syndrome (ACS) is currently diagnosed using clinical signs and invasive compartment pressure monitoring.

Hypothesis: NIRS can be used as a reliable method for the detection of an acute compartment syndrome.

Methods: 1) A prospective clinical trial of 102 patients at risk of an ACS were recruited. Continuous invasive pressure and NIRS measurements were recorded and compared.

2) A porcine model of 15 animals was used to investigate the influence of a subcutaneous and intra-muscular haematoma on the ability of NIRS to detect an ACS.

3) Two studies of volunteer subjects investigated the relationship between adipose thickness, measured by ultrasound, and the values of StO_2 provided by NIRS.

Results: 1) Correlation was observed between StO_2 and compartment pressure, however, inter-patient variability made the interpretation of the NIRS measurements difficult. This was improved by calculating the StO_2 difference between the injured and un-injured limbs.

2) In the presence of a sub-cutaneous haematoma, elevated values of StO_2 were demonstrated despite elevated compartment pressure and decreased intramuscular oxygen saturation.

3) Adipose thickness over the leg correlates with the StO_2 value and total haemoglobin in the light pathway in normal volunteers

Conclusions: A significant correlation between soft tissue oxygenation, measured non-invasively by near-infrared spectroscopy and invasively by compartment pressure was observed. Inter-patient variations in the StO_2 value made interpretation of clinical data difficult. The presence of a subcutaneous haematoma increased the StO_2 value despite elevated compartment pressure in the porcine model. The volunteer study demonstrated that an increase in the thickness of adipose tissue overlying the muscle compartment reduced the StO_2 value. Further investigation, using an increased number of NIRS parameters, examining total haemoglobin in traumatised tissue and reperfusion studies related to limb position and muscle contracture are warranted if the full potential of NIRS is to be realised.

TABLE OF CONTENTS **Page**

DECLARATION

Near-Infrared Spectroscopic Diagnosis of

Acute Compartment Syndrome

I hereby declare that I wrote this thesis and that the work described has been my own. I declare that it has not been submitted or accepted for any previous degree or professional qualification. The clinical and volunteer studies were carried out at the Royal Infirmary of Edinburgh. The animal work was carried out at The Moredun Research Institute, Penicuik, Midlothian. All quotations are distinguished by the use of quotation marks and sources of information are acknowledged.

This work was supported by funding from Hutchinson Technology Incorporated, Minnesota USA.

Matthew Hope 20th November 2006

ACKNOWLEDGEMENTS

I would like to thank Miss Margaret McQueen for providing me with the opportunity to carry out the work contained in this thesis. Without her experience, knowledge and enthusiasm this investigation would not have been possible.

Professor Hamish Simpson, my supervisor, has given me valuable feedback and constructive criticism during all the work. I am most grateful for his advice with regard to the animal model, both scientifically and administratively during a particularly difficult time in the animal and agricultural industries.

Carol Hajducka and Francis McPherson have been invaluable throughout this study. They have retrieved paperwork, entered clinical and volunteer data and arranged patient follow-up. The backup that they have provided allowed me to carry out the three studies presented here simultaneously so that the work could be completed in the time available.

I would like to thank Dr. R Elton, Edinburgh Royal Infirmary, for his analysis and statistical advice following the recruitment of the first 50 patients to the clinical study.

The patients who took part in this study must be acknowledged. It is hoped that this research allows something positive to be gained from their injuries. Thanks are also given to the nursing staff of the Edinburgh Orthopaedic Trauma Unit for their assistance with setting up equipment and time spent recording data and communicating any patient or monitoring problems to ensure the accuracy of the data.

I am very grateful to all the staff at Hutchinson Technology Incorporated (HTI), Hutchinson, Minnesota, USA for providing feedback and technical support for the investigational device. In particular thanks go to Barbara Gallea and LeAnn Anderson for many questions and interpretations, and Joop Jacobs and Rini Weyman for their persistent emphasis on basic research.

I would like to thank Dr Colin MacAldowie and his staff at the Moredun Research Institute for their help and advice in setting up and running the animal investigation.

The Orthopaedic Outpatients Department, Royal Infirmary of Edinburgh and Musculo-Skeletal Research Unit, University of Edinburgh has provided me with the facilities for additional research to be carried out.

For all the hospital staff that made the volunteer part of this investigation possible, I am very grateful and I hope the pen marks have now washed off. Particular thanks go to Carol Hajducka who recorded the measurements and Hanne Dornig who carried out skinfold thickness measurements.

I would like to thank Professor Jimmy Hutchison and Mr. David Finlayson, for providing inspiration and constructive feedback to encourage me to complete the writing of this thesis.

LIST OF ABBREVIATIONS

AC	Anterior compartment
ACS	Acute compartment syndrome
A&E	Accident and Emergency Department
AO	Arbeitsgemeinschaft fuer Osteosynthesefragen - Association for the Study of Internal Fixation
AT	Adipose thickness
BMI	Body Mass Index
cm	centimetres
ΔP	delta Pressure (mmHg)
Hb	deoxygenated haemoglobin
HbO_2	oxygenated haemoglobin
Hbt	total haemoglobin
IM	Intramedullary
Mb	deoxygenated myoglobin
MbO_2	myoglobin
MABP	mean arterial blood pressure (mmHg)
mA	milli-amperes
mm	millimetres
NIRS	Near-Infrared Spectroscopy
nm	nanometers
NMR	nuclear magnetic resonance
pCO_2	partial pressure of carbon dioxide
pH	measure of acidity or alkalinity of a solution ($pH = -\log_{10}[H_30^+]$)
pO_2	partial pressure of oxygen
ROC	Receiver Operator Curve
SC	Sub-cutaneous
SCBT	Sub-cutaneous border of the tibia
SD	Standard deviation
SEM	Standard error of the mean
StO_2	soft tissue oxygen saturation (%)

LIST OF TABLES **page**

LIST OF FIGURES **Page**

1. INTRODUCTION

1.1 ACUTE COMPARTMENT SYNDROME

1.1.1 Historical Background

Research during the last two centuries has provided us with many causes for the permanent disability that can follow limb injuries. One of these is acute compartment syndrome. Despite an increased understanding of the pathological processes involved, muscle weakness and contractures can still be seen in orthopaedic practice today, and the condition continues to stimulate discussion, research and medico legal interest.

Figure 1 Richard von Volkmann
(http://clendening.kumc.edu/dc/pc/volkmann.jpg)

Muscle contractures that develop rapidly following injury were reported in the mid-nineteenth century by von Stromeyer, 1840 and Guérin, 1842, but at this time they were believed to be the result of direct nerve injury (Griffiths 1940). Hildebrand in 1906 credited the earliest report of contractures that had developed following muscle ischaemia to Hamilton, 1850 (Griffiths 1940). It was Richard von Volkmann, however, who made the first detailed clinical descriptions of ischaemic muscle contractures. He published three accounts of acute-onset post-traumatic muscle contractures, the first in 1872 (Griffiths 1940). He contrasted the rapidity of onset and relentless progression of the ischaemic muscle contracture with that due to nerve injury, which developed late and responded to passive stretching. In his second paper,

1875 he believed that the contractures were due to 'inflammatory myositis'(Griffiths, 1940). The third paper (1881) provided the most detailed account. Volkmann proposed that the cause of the muscle contracture was ischaemic in origin and resulted from the interruption of the arterial blood supply to the muscle tissue. He reported cases arising from avulsion and ligature of major vessels as well as cases following the use of Esmarch bandaging. He believed the commonest cause however, was due to the application of tight bandages. In recognition of this work, a forearm contracture due to muscle ischaemia is commonly referred to as a 'Volkmann's ischaemic contracture'. In 1884, Leser described seven cases of ischaemic contractures and detailed an early canine experiment (Jepson, 1926). He postulated that the contractures were due to deprivation of oxygen to the muscles.

Peterson in 1888, disputed the theory of 'external pressure from bandaging' when he published a case report of a four year old girl. This patient had sustained an open supra-condylar fracture of the humerus. This was treated conservatively without the use of tight bandaging. She then developed ischaemic muscle contractures of the forearm that were confirmed at operation. Attention was drawn to ischaemic contractures in the United Kingdom by Dudgeon in 1902 who reported four of his own cases. He emphasised that this condition was not uncommon, but that it was merely underreported. He believed that the deformity was caused in many cases by tight bandaging and the pressure of splints. By 1909 Thomas had collected 107 published cases of contracture due to muscle ischaemia. Among these patients, he found 16 cases that had occurred in the absence of a fracture and 27 cases that had arisen without the application of splints or plaster of Paris. This confirmed that neither fractures nor occlusive dressings were essential precursors to an ischaemic contracture. The first suggestion that raised tissue pressure could result in

muscle ischaemia was made by Hildebrand (1906). He believed that muscular swelling caused arterial compression and subsequent ischaemia.

Bardenheuer (1911) provided a detailed account of the development of muscle ischaemia. He compared contracture development due to acute ischaemia secondary to haemorrhage with that caused by 'subfascial tension'. The presence of fascial compartments was described in his paper and he was the first to detail how the fascia can be incised, now known as fasciotomy, to relieve pressure within the compartment. In addition, it is pointed out that the release of pressure should be carried out before pulses become absent. This paper demonstrates the great depth of understanding of these contractures in Europe at this time. These ideas were expanded by Murphy (1914) who recognised that haemorrhage and effusion into muscular tissue would cause 'pressure ischaemic myositis'. The increase in pressure was then compounded by the constriction provided by a splint, bandage or tight skin. He proposed that all muscle damage occurred in the 'first seventy-two hours' after injury and stressed that best results are accomplished by early splitting of the fascia on the antero-ulnar side of the forearm.

The inter-war years saw the publication of animal experiments that aimed to identify the aetiology of ischaemic contractures. Von Nario, in 1925, reported a canine model of axillary artery ligature followed by injection of the arterial tree with sodium salicylate to produce an endarteritis obliterans. Some limbs developed gangrene, others developed contractures. In another experiment he repeated the ligatures but then added bandages. Those limbs bandaged for longer than 48 hours developed gangrene, whilst in those bandaged for less than 48 hours, ischaemic contractures developed that were histologically the same as those found in humans. He concluded that Volkmann's contracture was caused by diffuse arteriolar obliteration and that treatment should encourage collateral circulation and that the role of surgery was limited to contracture

prevention by the transplantation of muscle insertions. Jepson (1926), working at the Mayo Foundation (USA), also reported canine experiments that produced a hind leg contracture but his work used both venous occlusion as well as tight bandaging. He showed that by drainage of the venous collection and reduction of the 'intrinsic pressure', the deformity could be reduced. He suggested that early removal of a venous collection could be of value in preventing the development of the subsequent contractures. Wertheimer and Frieh (1937) produced a muscular infarction in animals by venous occlusion alone using injection of a charcoal suspension in gelatine. They concluded that obstruction of the venous circulation must also be involved in the aetiology of Volkmann's ischaemic contractures. Putti (1930) disputed the vascular theorists after publishing a series of 58 cases of contracture. He believed that the primary problem was damage to peripheral nerves and operative intervention should aim to improve the condition.

A study of the development of six cases of forearm ischaemic contracture (Tavernier 1936) showed that the position of the hand changed from a 'nervous' paralysis to one caused by forearm flexor muscle contracture over 18 months. Surgical observations demonstrated that the lesions affected all structures within constrained bony and fibrous limits. This included muscles, connective tissue and main nerve trunks. He pointed out that the infarcts that are seen may be of arterial, venous or vasomotor origin or may be the result of direct compression. He strongly recommended early operative intervention as soon as the syndrome appears to prevent the development of irreversible damage.

Around the period of the Second World War the theory of arterial obstruction proposed in some of the earlier animal work was felt to be the primary cause for the development of ischaemic contractures in clinical practice (Kappis, 1938; Griffiths, 1940;

Foisie, 1942). Griffiths published a report of 29 cases of forearm contractures after fractures and three cases following embolectomy. He reported a frequent intra-operative observation of brachial artery spasm or division leading to absent radial pulsation in the supracondylar fractures of the elbow. The absence of significant antecubital haematoma in these cases conflicted with the earlier venous occlusion theories. He placed considerable importance on three patients out of a series of 21 who had developed contractures in the 48-hour period following embolectomy for acute arterial obstruction. One of these patients later died from sepsis after a further embolism thus allowing histology to be obtained. This confirmed the presence of muscle necrosis and matched that found in earlier cases of Volkmann's ischaemic contracture. He concluded, '*In the light of these other cases and of the clinical and operative evidence, they bring conclusive proof that Volkmann's contracture is due to arterial occlusion and to nothing else.*' The concept of arterial occlusion as the primary cause of the contractures was strengthened by evidence from animal work on rabbits (Kinmonth *et al.,* 1949; Kinmonth 1952). Both the femoral and brachial arteries were found to be sensitive to minor trauma to the vessel wall resulting in a reduction in vessel diameter. The constriction continued for 1-2 hours after the insult and the response was found to be independent of local neural reflexes. This is believed to be the mechanism causing arterial spasm in supracondylar fractures of the humerus.

The papers published at this time, in believing arterial spasm to be the sole cause of ischaemic muscle contractures rather than increased intramuscular pressure, led to the misconception that contractures can only occur in the absence of a distal pulse. This erroneous belief can still on occasions be found in clinical practice today.

The majority of the early-published work focused on ischaemic contractures of the paediatric forearm. This interest had followed in response to Volkmann's original description. Ischaemic muscle contractures of the lower legs had been included in a number of series but were paid very little attention (Dudgeon, 1902; Thomas, 1909; Putti, 1938). The reported causes included polio, popliteal artery embolus and open tibial fracture with subsequent 'suppuration'. These cases were reported to have occurred in adults as well as children. The numbers of lower limb cases were small and no logical pattern was apparent, in contrast to those that developed contractures following the paediatric supracondylar humeral fracture. Ellis (1958) published a series of 343 adult tibial fractures and identified nine patients with muscle contractures without arterial injury. These patients all had sustained moderate to severe soft tissue injuries, and six had been treated using calcaneal traction. It was Seddon however who published the first paper dedicated to 'Volkmann's ischaemia of the lower limb' in 1966. He reported 15 cases that had received either a lower limb operation or an injury, four of which were tibial fractures. Five cases had an identifiable arterial disruption proximally, but the remainder had muscular infarcts without arterial injury. He emphasised the importance of early detection of signs indicating ischaemic muscle and that division of the deep fascia may be helpful in saving threatened muscle. Seddon recognised the distinction between cases that required femoral or popliteal artery repair and those with isolated muscle ischaemia. McQuillan and Nolan (1968) divided their series of 37 trauma cases into total ischaemia (arterial injury) and local ischaemia. They proposed that the term 'osteofascial compartment syndrome' should be retained only for injuries caused by 'excessive use'. They observed that patients with localised muscle ischaemia had peripheral pulses present initially, but later these became absent. A satisfactory outcome was achieved when

decompression of the swollen muscle was carried out by longitudinal incisions through the skin and fascia. The outcome was less favorable if there had been a delay to operation.

Matsen in 1975 recognised that the syndrome of muscle ischaemia and contractures was the final common pathway for many conditions that cause prolonged increases in intracompartmental pressure. He defined a "compartment syndrome" as '*a condition in which the circulation and function of tissues within a closed space are compromised by increased pressure within that space.*' The definition encompasses many of the earlier theories of muscle ischaemia and nerve dysfunction. This concept has now been accepted into clinical practice and compartment syndromes, both acute and chronic, have been described for many enclosed spaces throughout the body.

1.1.2 Pathogenesis

Starling (1896) showed that interstitial fluid was formed by the efflux of water and dissolved crystalloids as a result of the hydrostatic pressure within the capillary (Holden, 1975). The plasma oncotic pressure, produced by the retained plasma colloids, causes a compensatory influx of water, thereby maintaining the balance. An insult to the soft tissues, such as direct muscle injury, energy transfer following a fracture, or ischaemia due to arterial damage will lead to a localised inflammatory response and vasodilatation (Holden, 1975). The inflammatory response, mediated by release of chemotactic factors and accumulation of neutrophils (Sadasivan *et al.*, 1996; Schaser *et al.*, 1999), leads to an increase in capillary permeability and fluid leakage into the tissues. The fine 'balance' is disturbed, due to the accumulation of increased amounts of interstitial fluid. If the increase in fluid volume is constrained by a rigid compartment that prevents expansion then the intracompartmental pressure will rise. The effect of the increase in intracompartmental pressure has been shown by a number of investigators to cause a subsequent reduction in the perfusion to the compartment contents (Rorabeck *et al.*, 1972; Ashton, 1975; Matsen, 1975). Decreases in the perfusion to the compartment contents will cause an additional hypoxic insult to the tissue. This results in a continued inflammatory response and continued capillary leakage, creating a further rise in compartment pressure (Figure 2).

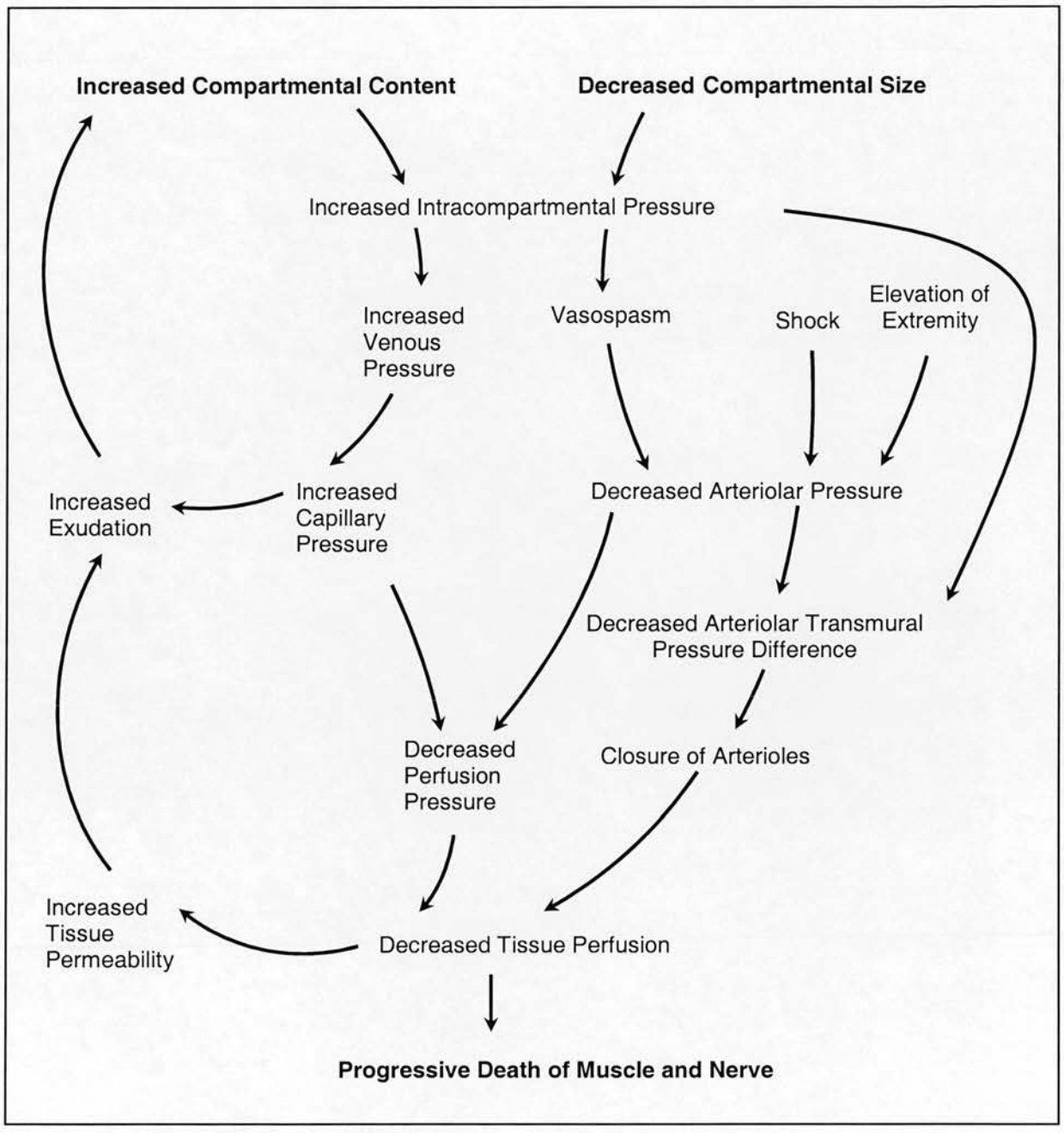

Figure 2 Pathophysiologic events that may occur in a compartmental syndrome. (Matsen, 1975)

Authors have debated the exact mechanism by which the blood flow is reduced. Ashton (1975) proposed active closure of small arterioles under vasomotor tone combined with passive collapse of soft walled capillaries in response to rising tissue pressure. Capillary occlusion alone, however, has been postulated as the cause of reduced blood flow (Hargens *et al.*, 1978). Matsen and co-workers (1980) believed that a reduction in the pressure gradient across the tissue bed was the cause for the fall in compartment perfusion. A small rise in tissue pressure has been shown to cause a reduction in venule diameter that is associated with cessation of blood flow within the venule. The rise in pressure within the venule will decrease the arteriovenous gradient across the capillary bed and hence the blood flow (Vollmar, 1999).

Many authors have investigated the decrease in compartment blood flow in response to increasing pressure. A precise 'closing' pressure has not been identified. Animal models of acute compartment syndrome have revealed that an intracompartmental pressure of 40 – 60 mmHg causes a steep fall in blood flow (Rorabeck and MacNab, 1975; Sheridan and Matsen, 1975; Rorabeck and Clarke 1978). These experimental compartment pressures are below both the diastolic and the mean arteriolar pressures. Whitesides (1975), using his own observations and ideas from other experimental work, emphasised the importance of 'compartmental perfusion pressure' that is dependant on the relative pressures of the compartment and systemic blood pressure. Whitesides and co-authors (1975) proposed that intracompartmental blood flow is reduced or absent at 10 – 30 mmHg below diastolic blood pressure.

The effect of decreased perfusion in a compartment syndrome, regardless of the exact mechanism, eventually produces cellular damage. Initially, an acute inflammatory reaction and later, degeneration of muscle cells can be seen (Sanderson *et al.*, 1975). The muscle degeneration, however, has been found to be partly reversible. This was

shown in a canine study where muscle was subjected to an intracompartmental pressure of 40 mmHg for eight hours. Despite initial muscle dysfunction, histological evidence of damage was absent at analysis four weeks later (Mortensen *et al.*, 1983). It is unclear if the reversibility is due to recovery or regeneration of new muscle fibres. The identification of factors that allow a greater degree of recovery and that determine the magnitude of the muscle injury are important for the clinical management of acute compartment syndrome. The magnitude of the intracompartmental pressure corresponds to the degree of muscle damage (Heppenstall *et al.*, 1988; Hargens et al., 1981; Matava *et al.*, 1994). In addition, the amount of muscle necrosis has been found to be proportional to the duration of elevated compartment pressure (Sanderson *et al.*, 1975; Heppenstall *et al.*, 1988). The two factors, time and compartment pressure, are therefore closely related. The influence of concomitant direct muscle injury on the development of muscle necrosis has also been investigated. Muscle subjected to direct trauma has an increased susceptibility to necrosis in the presence of raised intracompartmental pressure (Heppenstall *et al.*, 1986). Heppenstall has compared the degree of muscle necrosis seen in an acute compartment syndrome with that of an arterial injury. He demonstrated that the muscle damage produced by an experimental period of arterial occlusion is less severe than that produced by an acute compartment syndrome of the same duration (Heppenstall *et al.*, 1986).

A progressive increase in the intracompartmental pressure leads to dysfunction of the neuromuscular unit. At first muscle function is lost, followed by loss of function in nerves traversing the compartment (Rorabeck and Clarke, 1978). There remains considerable debate as to the level of intracompartmental pressure and duration that leads to a permanent loss of neuromuscular function. A pressure of 50 mmHg has been shown to interrupt median nerve function when maintained for greater than 25 minutes in

normotensive individuals (Gelberman, 1983). On the other hand, a pressure of 30 mmHg maintained for 8 hours will cause permanent muscle necrosis in dogs (Hargens *et al.*, 1981).

Reference is frequently made to the role of systemic blood pressure. Gelberman (1983) reports that in one 'hypertensive' individual (BP 130/90) median nerve conduction was not completely blocked despite a pressure of 60 mmHg for 120 minutes. A critical pressure threshold for the development of muscle necrosis was identified as being 20 mmHg less than diastolic blood pressure (Matava *et al.*, 1994). This finding is consistent with the earlier report of reduced compartment perfusion at 10-30 mmHg less than diastolic blood pressure (Whitesides, 1975). The importance of referencing the compartment pressure to blood pressure is now well accepted, but discussion still persists as to its precise use in relation to clinical management of patients.

In addition to the effects on soft tissues, elevated compartment pressure slows fracture union. The finding of delayed and non-union of fractures has been more frequent following an acute compartment syndrome (Karlstrom *et al.*, 1975). Court-Brown and McQueen (1987) validated this observation by demonstrating an increased union time in tibial fractures of 19 weeks following an acute compartment syndrome. An increased duration and severity of an acute compartment syndrome, represented by a delay to decompression and the development of late sequelae, have also been associated with delayed tibial union. The delay in bone healing has been attributed to a reduction in bone blood flow that occurs in an acute compartment syndrome (McQueen, 1995). A reduction in local perfusion and hence delivery of oxygen stimulates anaerobic respiration and a fall in intracellular pH as the intracompartmental pressure rises (Heppenstall *et al.*, 1988). Fracture healing is dependant upon a specific sequence of changes in the local pH. Magnetic resonance imaging has demonstrated that the

deposition of callus occurs during the later alkaline phase of the fracture haematoma at a pH of 7.5 (Newman *et al.*, 1985). It is not known if the early fall in pH in an acute compartment syndrome affects the later alkaline phase of callus formation.

1.1.3 Epidemiology

There are many causes of acute compartment syndrome, although in practice a combination of initiating factors can frequently be identified. A universal system for classification for acute compartment syndromes has not been proposed. More commonly, an acute compartment syndrome is described in terms of anatomical location and aetiology. Examples are summarised in Table 1.(Tiwari *et al.*, 2002). Acute compartment syndromes can be divided into two principal categories, those affecting the limbs and those affecting the abdomen. Abdominal compartment syndrome will be briefly mentioned below for comparison; thereafter, this thesis will focus on acute compartment syndrome of the limbs.

In parallel with the dysfunction of the muscular contents in a limb compartment syndrome, acute renal failure was found to be associated with raised intra-abdominal pressure (Harman *et al.*, 1982). The effects of abdominal compartment syndrome were found not to be restricted only to the peritoneal cavity but to also influence the function of important extra-abdominal organs (Cullen *et al.*, 1989). The syndrome is characterised by a tensely distended abdomen, raised intra-abdominal pressure, increased peak airway pressure, inadequate ventilation with hypoxia and hypercarbia, disturbed renal and cardiovascular function. Symptoms of abdominal compartment syndrome are frequently unhelpful as patients are often undergoing treatment on an intensive care unit.

Limb	
Orthopaedic	Tibial fracture
	Forearm fracture
Soft tissue injury	Prolonged limb compression / elevation
	Crush injury
	Burns
Iatrogenic	Vascular puncture in anticoagulated patients / haemophiliacs
	Intravenous / intra-arterial drug injection
Vascular	Ischaemia-reperfusion injury
	Haemorrhage
	Phlegmasia caerulea dolens
Abdominal	
Trauma	Blunt
	Penetrating
Haemorrhage	After surgery
	Ruptured abdominal aortic aneurysm

Table 1. Causes of acute compartment syndrome (Tiwari *et al.*, 2002)

The diagnosis of abdominal compartment syndrome is confirmed by the presence of raised intra-abdominal pressure along with decreased renal and respiratory function. Indirect measurement of intra-abdominal pressure using indwelling bladder catheters has been found to be accurate, and thus avoids the introduction of a catheter into the peritoneal cavity. An intra-abdominal pressure suggested for decompression is an absolute pressure above 25mmHg (Kron *et al.*, 1984). This is in contrast to investigators of limb acute compartment syndrome who relate the compartmental pressure to systemic blood pressure in order to calculate a tissue perfusion pressure for decompression.

In order to increase the level of accuracy of any diagnostic method, knowledge of the injuries and types of patients most at risk of an acute compartment syndrome is essential. McQuillan and Nolan (1968) reported 15 cases of localised upper and lower limb ischaemia following injury. Twelve patients had sustained a fracture, of which nine were of the tibia. The remaining three patients had developed localised ischaemia following a soft tissue injury alone. Reported incidences of fracture causing an acute compartment syndrome range from 34% in a study that included post ischaemic compartment syndrome (Sheridan, 1976) to 90% in a study of 55 children (Mubarak 1979). In a study of 151 cases of acute compartment syndrome, fractures had occurred in 75% (McQueen *et al.*, 2000). The commonest site for acute compartment syndrome was the leg (Table 2). This was the most frequent site whether or not a fracture had occurred. The frequency of acute compartment syndrome at other sites was similar in both groups. The most significant difference between patients with and without fractures was found in the thigh, where an acute compartment syndrome was more common following a soft tissue injury than a femoral fracture (Hope and McQueen, 2004).

Site of Acute Compartment Syndrome	No Fracture n = 38 (25%)	Fracture n = 113 (75%)
leg	20 (53%)	70 (62%)
forearm	9 (24%)	30 (26%)
thigh	6 (15%)	4 (4%)
hand	1 (2%)	5 (4%)
foot	2 (5%)	4 (4%)

Table 2. Site of limb acute compartment syndrome following injury. (Hope and McQueen, 2004)

Early evidence as to the incidence of acute compartment syndrome in tibial fractures was provided by the observation of ischaemic contractures. Ellis (1958) reported a 4% incidence of contracture in 235 tibial shaft fractures. Nicoll (1964) observed ischaemic contractures having occurred in 1.3% of 343 tibial shaft fractures and related these to treatment in tight plasters and high tissue pressure beneath rigid fascial structures. Both authors made similar observations. Ellis observed an association between the severity of soft tissue injury, treatment with calcaneal traction and development of contractures, whereas Nicoll noticed an association between the soft tissue injury, calcaneal traction and development of ankle stiffness. The patients with severely injured soft tissue were more likely to have poor long-term functional results. Acute compartment syndrome occurred in association with open fractures on three occasions in 37 cases of

ischaemia complicating an injury (McQuillan and Nolan, 1968), and on two occasions in 24 compartment syndromes after tibial fracture, where it was postulated that the fascial disruption provided some protection from the increasing pressure (Rorabeck and McNab, 1976). A retrospective review of 198 open tibial shaft fractures in multiply injured patients demonstrated an acute compartment syndrome in 9.1% of cases. Of the 198 cases, 86% occurred after a road traffic accident and 64% were Grade III open (according to the soft tissue injury - Gustillo and Anderson, 1976). In contrast, the study carried out in Edinburgh in the period 1988 to 1992, demonstrated an incidence of acute compartment syndrome of 4% in closed tibial fractures and 1% for open tibial fractures (McQueen *et al.*, 2000). In this series, which did not include children, the mean age of acute compartment syndrome was found to be 32 years (14 to 88 years) and in a similar study of 49 patients (Sheridan, 1976) it was 29 years (6 to 80 years). The distribution of patients, however is not evenly spread throughout the range, but is maximal in frequency in the late teenage years and drops progressively through the adult years. The male to female ratio was 10:1 (McQueen *et al.*, 2000). A review of the causes of acute compartment syndrome reveals that road traffic accidents are the most frequently implicated in patients with a fracture (Table 3). Low energy sporting injuries were also a common cause of acute compartment syndrome in both those with and without fractures. Patients without fractures had sustained a variety of soft tissue injuries and in some were associated with coagulation defects. Acute compartment syndrome in the absence of a fracture has also been reported to occur spontaneously in diabetic patients (Smith, 1999; Chautens, 1997), following elevation in the hemilithotomy position (Tan *et al.*, 2000) and after lifting a heavy load (Kapoor, 2000).

In addition to the causes described above, an acute compartment syndrome can arise in a limb in association with a crush syndrome or reperfusion injury following

arterial revascularisation. A crush syndrome occurs when the muscle necrosis secondary to raised intracompartmental pressure leads to acute renal failure, haemodynamic and metabolic compromise. The underlying cause can often be overlooked due to the distraction caused by the presentation and management of the systemic complications and as a result, a delay to treatment of the acute compartment syndrome can arise (Shaw, 1994). In the series studied in Edinburgh, there were 13 cases of crush syndrome referred during an 8-year period. This accounted for 8% of all acute compartment syndromes treated (Hope and McQueen, 2004). Post-ischaemic compartment syndrome, following revascularisation procedures, occurs due to tissue swelling during the post-operative period, maximal around the 6^{th} – 7^{th} days (Patman, 1975). Risk factors have been identified and continuing compartment pressure monitoring has been observed not to alter management (Scott *et al.*, 1988). Crush syndrome and reperfusion injury are important causes of compartment syndrome, but both demonstrate disturbed systemic and local physiology. In order to investigate a potential new technique for compartment monitoring, normal physiology is required to identify sources of error more easily and therefore, these causes of acute compartment syndrome have not been included in this investigation.

Aetiology of Acute Compartment Syndrome	**No fracture** (n=38)	**Fracture** (n=113)
Sport (football/rugby/skiing)	10 (26%)	30 (27%)
RTA	2 (5%)	26 (23%)
RTA (pedestrian)	2 (5%)	17 (15%)
Fall	2 (5%)	15 (13%)
Crush injury	8 (21%)	10 (9%)
Fall from height	0	9 (8%)
Assault	1 (3%)	4 (4%)
Stab wound	4 (11%)	0
Gunshot wound	1 (3%)	0
Intra-arterial injection	2 (5%)	0
Coagulation defect	4 (10%)	2 (2%)
Infection	1 (3%)	0
Spontaneous	1 (3%)	0

Table 3. Aetiology of limb acute compartment syndrome following injury. (Hope and McQueen, 2004)

1.1.4 Diagnosis

Classically, a clinical diagnosis of an acute compartment syndrome is based on the observation of clinical signs that arise due to the presence of hypoxic muscle and nerve tissue. The most frequent clinical sign is of pain, ischaemic in nature, which is out of proportion to the injury that has occurred. In a series of 15 cases of acute compartment syndrome, 14 were found to have increased pain (McQuillan, 1968). In another series of 19 patients, the finding of deep unrelenting pain was also a predominant feature of forearm acute compartment syndrome (Eaton and Green, 1975). It was not a universal finding, however, as two patients developed contractures in the absence of significant pain. Pain was again reported as a feature in 12 patients with forearm acute compartment syndrome (Gelberman, 1981). The pain is made worse by passive stretching of the muscles involved. Pain with passive stretching can be difficult to demonstrate particularly in the presence of a significant soft tissue injury and also if the fracture is not well supported, the forces required to stretch the muscle will cause the fracture to deform and elicit pain giving a falsely positive sign. Gelberman noted that both rest pain and pain on passive stretching was only reproducible in the patients who were fully conscious. The clinical sign of pain can also be difficult to evaluate in uncooperative children (Mars and Hadley, 1998) and can be masked by opiate analgesia (Harrington *et al.*, 2000) as well as altered consciousness. Nerve ischaemia is indicated by the development of paraesthesia in the cutaneous distribution of nerves that traverse the compartment involved, and an early series reported 100% alteration in sensation (Eaton and Green, 1975). Altered distal sensation was a feature in 50% of acute compartment syndrome patients with a fracture, whereas without a fracture it was present in only 36% (Hope and McQueen, 2004). Muscle paralysis arises late and is demonstrated by weakness of the muscles of the

involved compartment. It is thought to be due to either prolonged nerve ischaemia of the relatively insensitive motor fibres or as a result of direct damage to the muscle fibres. Paralysis of the compartment muscle is known to be associated with poorer recovery (Bradley, 1973). It is common to find a tense compartment on palpation, but a tight swollen limb can exist without an acute compartment syndrome and similarly an acute compartment syndrome may be present in a deep compartment in isolation or hidden by overlying oedema, casts or bandaging. An acute compartment syndrome occurs in the presence of distal pulses. The finding of absent distal pulses, contrary to earlier belief, indicates an arterial injury and therefore warrants vascular referral and investigation by angiography. In the case of an elevation in intracompartmental pressure to the level of systolic blood pressure then the distal pulse could be reduced.

Despite knowledge of the clinical signs and symptoms of acute compartment syndrome, presentations can be misleading and particularly difficult in the obtunded or confused patient. The resulting difficulty in diagnosis can lead to a delay in receiving treatment. As early as 1926, Jepson suggested that treatment, without delay, in the form of release of the compartment contents could avoid muscle contracture. It has been shown that a delay to decompression is associated with increased risk of late sequelae (McQuillan and Nolan, 1968; Sheridan and Matsen, 1976; McQueen *et al.*, 1996; Mullet *et al.*, 2001). Sheridan and Matsen (1976) demonstrated that decompression within 12 hours resulted in normal function in 68% of cases, compared to only 8% if fasciotomy was carried out after 12 hours. The recommendation of early decompression of acute compartment syndrome, repeated by many authors, can only be achieved if the diagnosis has also been made early.

In order to assist at times when the clinical diagnosis was difficult, Thomas Whitesides (1975) published a method of measuring compartment pressure using an 18-guage needle connected to saline filled tube and mercury manometer. He illustrated his

paper with cases where tissue pressure measurements have prevented unnecessary fasciotomies as well as allowing an early confirmation of a compartment syndrome when the clinical diagnosis was equivocal. This measurement technique, however, potentially allows falsely elevated readings due to increased pressure at the needle tip as a result of the injection of saline (Mubarak *et al.*, 1976). Matsen (1976) proposed a method to determine intracompartment pressure by measuring the pressure required to slowly infuse saline into the compartment. Despite a high level of accuracy, this method has the potential risk of causing an increase in the compartment pressure itself by the continuous infusion of saline into the muscle. In order to overcome the difficulty with falsely elevated readings due to the infusion of saline, Mubarak (1976) described a further technique of pressure measurement. He proposed inserting a fine catheter through which a braided wick was passed to lie within the tissues just beyond the end of the catheter. The presence of the wick allows the formation of micro-columns of fluid between the tissue and the column of saline within the catheter thereby preventing the problems of tissue or air-bubble occlusion at the catheter tip. Without the technical step of introducing a wick into the catheter, the slit catheter technique, reported by Rorabeck *et al.* (1981), allows a greater area for monitoring and reduces the chances of tissue occlusion. It is this technique that was used to measure the compartment pressures in this investigation. Electronic devices are also available for the measurement of intracompartment pressure. These can either be in the form of single pressure recording or continuous measurement, both of which also require the introduction of a needle or catheter into the compartment. A recent study has compared three different techniques of compartment pressure monitoring *in vitro* and found that the manometer tubing with saline and slit catheter to be the most accurate (Boody and Wongworawat, 2005).

In addition to the controversies concerning the technique for pressure measurement, the question of correct location for the catheter tip has often been raised. Investigation of resting forearm pressure in normal volunteers has revealed that differences of 5 mmHg may occur over distances of as little as 4 cm. (Seiler *et* al., 1993). In the clinical setting, variations in pressure were investigated in 25 volunteers with tibial fractures. Pressure recordings were carried out at 5 cm intervals along the length of all lower limb compartments (Heckman *et al.*, 1994). The highest pressures were recorded within a few centimeters of the fracture, with values dropping rapidly further than 5 cm from the fracture. A recommendation was made to record pressure at the fracture site and at more than one site in both the anterior and deep posterior compartments when a compartment syndrome was suspected clinically.

The measurement of intracompartment pressure, whatever technique is used, provides the observer with a value. The interpretation of this value and decision regarding surgical decompression is then dependant on the individual surgeon. Previous studies have investigated a number of issues critical to this interpretation. Whitesides (1975) related the pressure to systemic blood pressure to provide an indication of the compartment perfusion. He recommended decompression when the tissue pressure reaches 25 – 30 mmHg lower than the diastolic blood pressure and in the presence of clinical signs of acute compartment syndrome. Some authors have suggested absolute compartment pressure values, independent from the systolic blood pressure, should be used as the threshold for decompression. Canine studies suggested a threshold for decompression at a value of 30 mmHg (Hargens *et* al., 1981). This value was used as the threshold for decompression in 11 out of 27 patients who were clinically suspected of having an acute compartment syndrome (Mubarak *et* al., 1978); 30 mmHg was also used as the threshold for decompression in the forearm (Gelberman *et* al., 1980). Absolute

pressures up to 45 mmHg have also been quoted for threshold values (Matsen, 1980). Following on from the work of Whitesides (1975), more recent studies have recommended that pressure recordings should be carried out in comparison with the systemic blood pressure. The difference between the blood pressure and the compartmental pressure is represented by the term 'ΔP' (mmHg). Some authors have used the mean arterial blood pressure (MABP), whereas some choose to use the diastolic blood pressure alone to represent the perfusion pressure. In a canine compartment syndrome model, Heckmann (1993) compared animals with differing values for ΔP and concluded that decompression should be carried out if the compartment pressure reaches within 10-20 mmHg of the diastolic pressure. Similarly a canine model was used to recommend decompression at a level of ΔP of 30 mmHg (using MABP). This value of ΔP was increased to 40 mmHg if the muscle had been traumatized or subjected to ischaemia (Heppenstall *et al.,* 198; Bernot *et al.,* 1996). A prospective study of 116 tibial diaphyseal fractures addresses the issue of absolute pressure versus ΔP for the threshold for decompression (McQueen and Court-Brown, 1996). Continuous monitoring using the slit catheter technique was carried out for 24 hours. The threshold for decompression was set at a ΔP of less than 30 mmHg (using the diastolic BP). In the first twelve hours, 53 patients had absolute pressures greater than 30 mmHg, 30 patients were over 40 mmHg, but only one had a ΔP of less than 30 mmHg, and he had a fasciotomy. At six months, no patients had sequelae of acute compartment syndrome. This study demonstrates how the ΔP can indicate the need for decompression, but also shows the protective value of the ΔP, provided the value remains greater than 30 mmHg.

Compartment monitoring is currently accepted for patients who are difficult to assess such as children, head injured or obtunded patients, and the multiply injured patient. Those determined to be 'at risk', predominantly male patients in their teens and

twenties who have tibial shaft fractures, high energy distal radial fractures or injuries in coagulopathic patients are also recommended to undergo compartment monitoring (McQueen *et al.,* 2000). In comparing continuous monitoring with clinical diagnosis alone, it was found that continuous compartment pressure monitoring allowed a decompression to be carried out at a mean of 16 hours earlier in the monitored group. The reduction in delay to fasciotomy was also associated with a significant reduction in the sequelae and time to fracture union in the monitored group (McQueen, *et al.,* 1996).

Following these recommendations, orthopaedic practice in the United Kingdom with regard to compartment pressure monitoring has been reviewed by means of a postal questionnaire (Williams *et al.,* 1998); 100 orthopaedic surgeons were randomly selected and 78 replied to the questionnaire. Thirty-six surgeons said they had equipment to measure compartment pressure; only 12 of these used it routinely. Thirteen consultants had performed fasciotomies when the compartment pressure had been normal, and eight had decided not to carry out a decompression in the presence of abnormally high pressure readings. Thirty-three respondents did not know what pressure they would carry out a fasciotomy and of the remainder, there was a wide variation in the threshold values for decompression. The majority of consultants favoured an absolute compartment pressure value rather than ΔP for decompression. The absence of monitoring equipment and lack of knowledge as to the pressure for decompression were cited as the two main reasons for not carrying out compartment pressure monitoring routinely in the United Kingdom. Janzing (2001) highlighted a potential problem of routine pressure monitoring when he reported a clinical study of 95 tibial fractures. He analysed a number of recommended pressure criteria, but could not identify any one with both satisfactory sensitivity and specificity. He warned that the routine use of a threshold pressure with a low sensitivity could lead to the over treatment of suspected acute compartment syndrome. He

recommended that monitoring be reserved for those who are symptomatic or who are difficult to assess.

Intracompartmental pressure measurements are invasive and therefore painful. In addition, the pressure provides an indicator but not a direct measure of the metabolic state of the muscle in question. A non-invasive and direct measure of metabolic activity would therefore be preferable. Metabolic changes in ischaemic muscle have been monitored by the non-invasive technique of phosphorus-31 nuclear magnetic resonance (NMR) spectroscopy (Newman, 1984). NMR spectroscopy provides a signal that reflects the intracellular levels of phosphocreatinine, adenine triphosphate and inorganic phosphate. From this data the intracellular pH can be calculated. This method has been used to validate pressure studies in acute compartment syndrome (Heppenstall *et al.*, 1989). The access to NMR facilities is still problematic in some centres and is not suitable for the continuous or perioperative monitoring of acutely injured patients. A non-invasive device for the measurement of compartmental pressure has been reported (Steinberg and Gelberman, 1994). The device measures surface hardness of tissues surrounding a muscle compartment in a similar fashion to the tonometer for determining intra-ocular pressure. In both a canine study and a clinical study, on six patients with acute compartment syndrome, a good correlation with the intramuscular pressure was achieved. Further clinical studies, however, have identified that this device has insufficient specificity to be recommended for the detection of acute compartment syndrome by non-invasive means (Dickson *et al.*, 2003).

1.1.5 Management

When an acute compartment syndrome becomes established, decompression of the involved compartment by division of the overlying skin and fascia is recommended. Volkmann (1881) noted the association between tight bandaging, casting and the development of contractures. Splitting and spreading of plaster casts has been shown to reduce intracompartmental pressure by 65% and a further 10% by release of the underlying dressings (Garfin *et al.,* 1981). Despite the observation made by Volkmann (1881), it is unclear whether the release of any external constricting dressings will prevent the development of an acute compartment syndrome, or will merely delay its progression. Similarly, development to an acute compartment syndrome may be influenced by the position of the injured limb. Elevation of the anterior tibial compartment 32 cms above heart level does not significantly change the intramuscular pressure, but reduces the perfusion pressure from 65 mmHg to 17 mmHg after 30 minutes (Zhang *et al.,* 2001). This moderate elevation in this human compartment syndrome model is accompanied by distal sensory changes that are not present when the pressurised compartment remains at heart level (Wiger *et al.,* 2000).

A conservative adjunctive treatment for an acute compartment syndrome has been suggested. In a canine compartment syndrome model, hyperbaric oxygen therapy was used to increase the oxygen concentration delivered to tissues. It also has a local vasoconstrictive effect that is believed to cause a drop in capillary pressure, which in turn allows a greater rate of resorption of tissue fluid. The study demonstrated a significant reduction in oedema formation and muscle necrosis compared to the muscle compartments maintained without hyperbaric oxygen treatment. It is suggested that this therapy may have a preventative role in the early part of a developing acute compartment syndrome

(Skyhar *et al.,* 1986). However, this potential adjunctive treatment has an obvious limitation due to very restricted access to treatment chambers.

Bardenheuer first described surgical decompression of the forearm for a developing Volkmann's ischaemia in 1911. Since this time different techniques have been described for compartment decompression in many regions of the body. The aim of surgical decompression in an acute compartment syndrome is the opening of all tight fascial envelopes. This should not be carried out through a limited incision as this has the potential disadvantages of inadequate decompression and the subsequent post-ischaemic swelling can lead to further compromised muscle proximal or distal to the incision beneath the intact skin (Cohen *et al.*, 1991). Following forearm volar decompression Gelberman (1980) recommended pressure measurements of the dorsal compartment and suggests dorsal decompression if the pressure exceeds 30 mmHg, whereas Matsen (1981) believed palpation of the forearm muscles was sufficient and if soft, no further decompression was required.

Techniques for decompression of the leg have been described by a number of authors. These involve either single or double incisions, as both can equally decompress all four compartments (Mubarak and Owen, 1977). Single incisions provide a better cosmetic appearance in the long term, but double incisions are quicker and are safer as less deep dissection is necessary. All authors agree that decompression of all four compartments is required. Kelly and Whitesides (1967) suggested fibulectomy through a single incision, focusing particularly on the deep posterior compartment. This procedure is no longer favoured due to residual discomfort and laxity, highlighted particularly by the experience following fibulectomy for grafting (Anderson and Green, 1991). The technique proposed by Mubarak and Owen (1977) is currently one of most frequently carried out. It is the technique used for all lower leg fasciotomies in this study. The

procedure involves a double incision. The anterolateral incision is placed half way down the leg, 2 cm anterior to the fibular shaft. The skin is retracted anteriorly allowing division of the fascia overlying the anterior tibial compartment. The skin is then retracted posteriorly to provide access for the fasciotomy over the lateral compartment. Care is taken to identify and protect the superficial peroneal nerve that emerges from the fascia in the distal half of the leg near the intermuscular septum before traversing anteriorly. The posteromedial incision is placed more distally in the leg, 2 cm posterior to the palpable posterior margin of the tibia. The incision is deepened anteriorly, avoiding the long saphenous nerve and vein to divide the fascia overlying the deep posterior compartment at the edge of the tibia. The fascia over the superficial posterior compartment is then divided separately by again retracting the skin posteriorly. Mubarak and Owen (1977) suggest 15cm incisions, followed by division of the fascia proximally and distally using blunt tipped scissors held curving away from any important structures. This is no longer recommended (Cohen *et al.,* 1991), as the incision must allow adequate decompression and visualization of the muscle. The determination of muscle viability is subjective. Observations are made of the muscle colour, its ability to bleed when it has been incised and its contractility following mechanical stimulation. It is necessary to excise any necrotic muscle. Any muscle that is of doubtful viability can be left and inspected at a later procedure. At the end of the procedure the wound is left open to prevent later increases in pressure and covered with sterile dressings. After approximately 48 hrs the wound is re-inspected and any necrotic muscle is excised.

A number of different methods of wound closure have been advocated. These include delayed primary closure, split skin grafting and skin edge closure devices. Delayed primary closure is possible if the swelling has resolved and the wound edges can be opposed without tension. When the edges cannot be brought together, some authors

advocate the use of rubber or non-absorble sutures as lacing or dermatotraction devices to draw the edges together as the swelling resolves (Wiger *et al.,* 2000; Chiverton and Redden, 2000). This allows the wound to be closed without the need for a split skin grafting over a period of five to ten days. Due to the delay in closure with traction techniques there is an increased risk of infection (Johnson *et al.,* 1992) and consequently some surgeons preferentially use split skin grafting to provide early wound cover. In one series split skin grafting was used to close 77% of fasciotomy wounds (Sheriden and Matsen, 1976). However, skin grafting itself has the disadvantages of donor site pain, unsightliness, altered sensation and muscle tethering (Fitzgerald *et al.,* 2000). The ideal solution to this problem has not yet been identified.

Complications of acute compartment syndrome are commonly seen when the diagnosis has been missed, the fasciotomy has been carried out late or the decompression has been incomplete. Sheridan and Matsen (1976) observed normal function in only 8% and complications developed in 54% who had undergone decompression later then twelve hours from diagnosis. Normal function was determined as the absence of any sensory or motor deficit. The sensory area affected depends on the compartment that has been involved. The motor loss is dependant on the site of muscle necrosis and subsequent scarring and contracture formation. In the leg, isolated involvement of the long toe flexors in the deep posterior compartment will cause toe clawing, but if all muscles are contracted a fixed equinus deformity will result. Similarly contracture of the anterior compartment muscles will result in loss of plantar flexion at the ankle. Isolated contracture of extensor hallucis longus has been reported as occurring in 5% of closed tibial fractures treated by reamed intramedullary nailing (Robinson *et al.,* 1999). The presence of these clinical signs is used as a marker for undiagnosed acute compartment syndromes. The complications that were identified by Sheridan and Matsen (1976) included infection of

soft tissue and bone, renal failure, amputation and death. In addition to this, delayed union of tibial fractures has been associated with delayed decompression (McQueen, 1995). In a report of five patients who underwent decompression later than 35 hours after injury, all patients were found to have complications (Finkelstein *et al.,* 1996). All developed localised infection, one patient died and the remainder required amputations. The authors suggested that the practice of delayed compartment decompression should be reassessed in view of the poor outcome. A delayed reconstruction may produce an improvement in function in the long-term.

An awareness of the poor outcome following complications of an acute compartment syndrome clearly demonstrates the need for early accurate diagnosis and treatment of this condition.

1.2 NEAR-INFRARED SPECTROSCOPY

1.2.1 Background

Infrared is a form of non-visible light that makes up part of the electromagnetic spectrum. All electromagnetic waves have the ability to transport energy through a medium (Figure 3). This property allows electromagnetic waves to be used in many medical as well as domestic applications. The specific task to which the wave can be applied is determined by its wavelength and frequency.

Light is part of the electromagnetic spectrum, which comprises the visible portions and the non-visible infrared and ultraviolet ranges. Visible light and ultraviolet light are absorbed predominantly at the skin surface, whereas infrared, having a longer wavelength, can travel deeper into the tissues. The depth to which photons can travel in biological tissues is dependant upon a combination of surface reflectance, scattering and absorption within the tissues (Jöbsis, 1977). The level of reflectance is largely dependant on the incident angle, whereas the scattering and absorption are properties determined by the wavelength. As the wavelength increases, the amount of scattering reduces which therefore favours infrared. Levels of absorption are dictated by the specific absorption characteristics of the molecules encountered within the tissues along the light pathway. Light over 1300 nm in wavelength is absorbed rapidly over only a few millimetres by water in the tissues. Light of wavelength less than 700 nm is scattered widely and then largely absorbed by haemoglobin molecules preventing any significant travel through the tissues. This allows light in the range 700 nm to 1300 nm to travel greater distances without significant absorption or scattering. Light in this range corresponds to red and near infrared light.

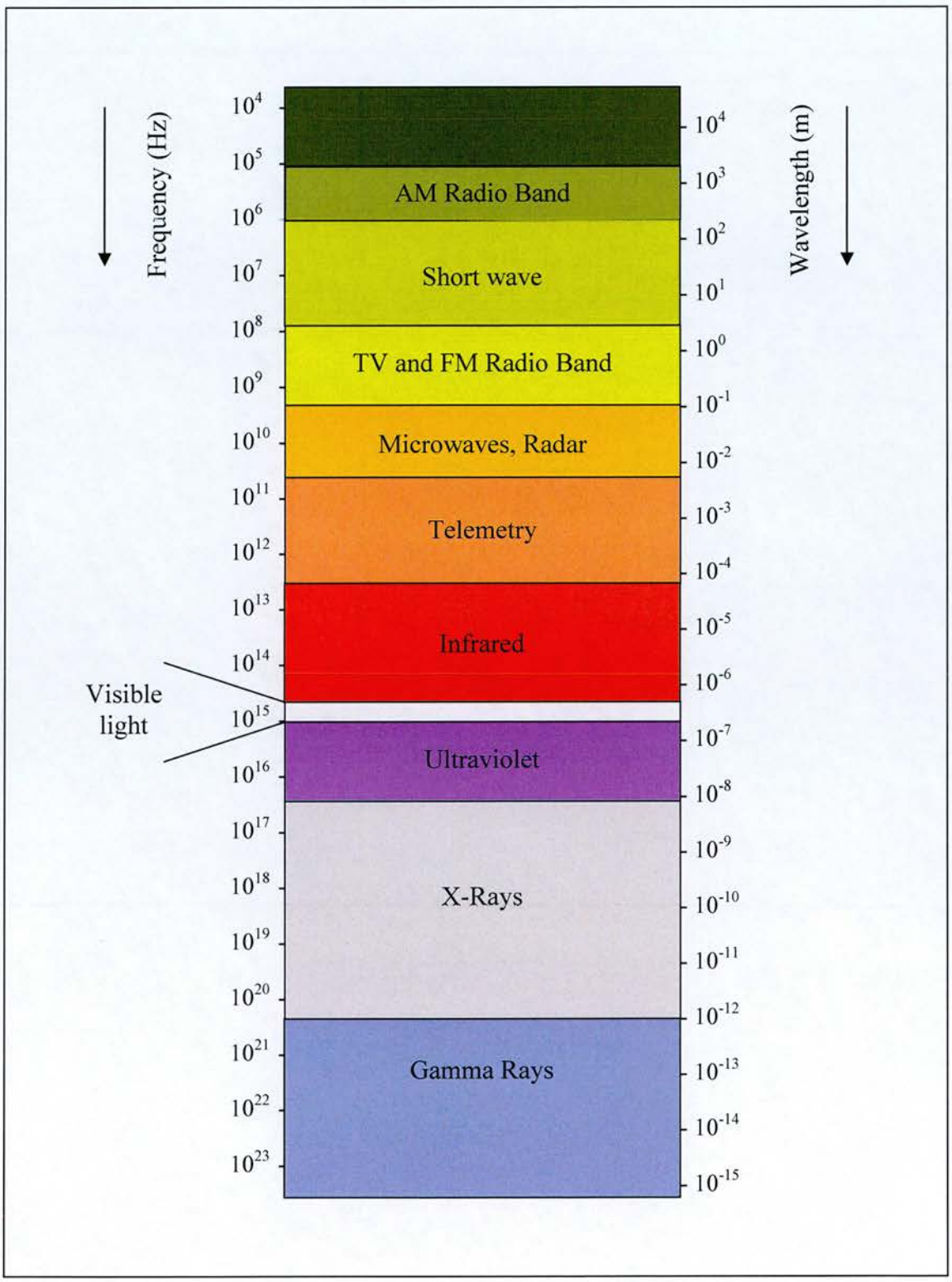

Figure 3 The electromagnetic spectrum

All substances have an absorption spectrum specific to their makeup. The German chemist Felix Hoppe-Seyler used this physical property in 1864 (Wahr *et al.*, 1996) when he demonstrated that oxygenated blood differed from deoxygenated blood by its absorption characteristics. This principle can be used to measure the concentration of a substance by observing how much light of a particular wavelength has been absorbed as it travels through tissue. This was formally described by August Beer (1851), working with the ideas of Heinrich Lambert and is known as the Lambert-Beer law (Wahr *et al.*, 1996). This states that the transmission of light through a solution is a logarithmic function of the density or concentration (C) of the absorbing molecules in the solution. The intensity of the transmitted light is determined by the path-length through the solution (D) and extinction coefficient (ε) for the material at a given wavelength. This law is written as follows:

$$I_{trans} = I_{in}e^{-D.C.\varepsilon}$$

Where I_{trans} = intensity of transmitted light, I_{in} = intensity of incident light and e = natural log base (2.71828) (Wahr *et al.*, 1996).

This law allowed the calculation of haemoglobin saturation in a cuvette carried out by Drabkin and Austin, 1946 (Wahr *et al.*, 1996). If the absorption spectra are known for a number of different molecules, then their concentration can be calculated simultaneously on a single sample. In muscle the most significant molecules that absorb near-infrared light are haemoglobin and myoglobin, which have indistinguishable spectra, and the copper atoms of the enzyme cytochrome a3 in the electron transport chain. These molecules demonstrate changes in their absorption spectra at specific wavelengths when bound to oxygen (Chance, 1954). Due to the overlapping spectra, the contribution from cytochrome a3 is believed to be only 10-15% of the total absorption in muscle tissue (Boushel and Piantadosi, 2000).

For use in tissues the Lambert-Beer law requires the following information: first, a wavelength value for each absorbing substance, second, a change in light intensity and finally, the length of the light pathway in the tissues. In making these measurements from biological tissues, the change in light intensity is influenced by the length of the light pathway in addition to the concentration of the molecules present. This is due to both the pathway geometry and scattering of light as more tissue is penetrated. In an instrument using direct transmitted light over a short distance, for example 5-7 cm, it was possible to investigate the cerebral circulation of cats (Jobsis, 1977). This method however is technically difficult over greater distances due to the longer light pathway and consequent loss of light intensity. By measuring the reflected light, it has been shown that the length of the light pathway is linearly related to the separation between the transmission and receiving points (optodes). Between the optodes on the skin surface it has been found that the light follows a curved pathway (Cui *et al.,* 1991). The scattering effect of biological tissue requires a modification of the Beer-Lambert law to incorporate a correction for the path-length and light losses due to scattering and absorption by other oxygen-independent molecules. These are known as the differential path-length factor and optical density respectively. They are incorporated into the equation, which is known as the modified Lambert-Beer law (Deply *et al.,* 1988). To measure multiple concentrations of molecules a set of linear equations is produced from the modified Lambert-Beer law. The resolution of these produces an algorithm that is used in the near-infrared spectrometer.

Near-infrared spectroscopic instruments can therefore be divided into two categories: saturation monitors and concentration monitors. Saturation monitors use transmitted light over a short distance and do not calculate the path-length in order to provide information using the ratio of substances such as oxygenated to deoxygenated haemoglobin. Concentration monitors are further subdivided into those that measure

relative concentration changes and those that aim to provide absolute concentration values. It is only the latter that requires the precise measurement of the light pathway (Wahr *et al.*, 1996).

1.2.2 Experimental Studies

The theory behind NIRS assumes that the contribution from haemoglobin and myoglobin are similar due to indistinguishable absorbance spectra. In order to be able to interpret the NIRS output, this assumption has been tested using nuclear magnetic resonance spectroscopy (NMR). NMR is able to differentiate between deoxygenated haemoglobin (Hb) and deoxygenated myoglobin (Mb). Observation has been made from the human lower leg of the changes in NIRS signal, deoxy Hb and deoxy Mb during 10 minutes of tourniquet ischaemia (Tran et al, 1999). The NIRS output, the deoxy Mb and the combined deoxy Hb and deoxy Mb levels fell by 80% over 10 minutes, whereas the deoxy Hb alone had a rapid fall of only 10% and then reached a steady state for the remainder of the ischaemic period. A second experiment with calf exercise showed a similar relationship, but the deoxy Mb only fell by 20%. The relationship suggests that the NIRS output over muscle is principally derived from intracellular oxygen and that the haemoglobin in the vascular space has little contribution. Mancini and his co-authors (1994) conducted a similar NMR and NIRS thigh tourniquet and exercise study using volunteer subjects, but only detected the presence of deoxy Mb in 1 of 4 subjects after exercise. The addition of ischaemia produced deoxy Mb peaks on NMR. They concluded that the change in NIRS output was exclusively produced from deoxy Hb, but did state that there was a small contribution from deoxy Mb.

Investigation has been made into the correlation between the venous oxygen saturation and levels of skeletal muscle deoxygenated haemoglobin and/or myoglobin measured by NIRS. Following incremental increases in workload on an exercise bike, femoral venous oxygen content was found to fall steadily (Costes *et al.,* 1996). The NIRS output, recorded over the vastus lateralis muscle fell initially, but then stabilised. The correlation between venous oxygen and NIRS was weak, suggesting that in part the venous Hb could account for the pattern but an additional local factor was influencing the NIRS signal. A Canadian study found a similar result (MacDonald *et al*, 1999). They observed that after an initial decrease, the NIRS measures of oxygen saturation over the muscle actually rose, whereas the femoral venous oxygen content fell steadily. They concluded that 'NIRS did not provide a reliable estimate of haemoglobin and/or O_2 saturation as reflected by direct femoral vein sampling.' These investigations suggest that NIRS may be influenced more strongly by muscle oxygenation rather than the oxygenation state of intravascular haemoglobin.

In addition to tissue oxygenation, NIRS can provide information about blood flow within the tissues. If it is assumed that the concentration of myoglobin in the NIRS light pathway over skeletal muscle is constant, then an additional parameter can be obtained from the NIRS signal. By calculating the sum of deoxygenated and oxygenated haemoglobin, a variable is derived that reflects the total amount of haemoglobin within the tissue. Alterations in the total haemoglobin indicate changes in the tissue blood volume and therefore the blood flow can be calculated from the rate of change in tissue blood volume. Forearm blood flow has been measured by NIRS and correlates closely with measurements made by venous occlusion plethysmograghy (Hampson and Piantadosi, 1988; Edwards *et al.*, 1993; De Blasi *et al.*, 1994). This knowledge has allowed the use of limb tourniquets to investigate the relationship non-invasively between blood flow and

muscle oxygenation. In a study of ten volunteers, an arterial arm tourniquet applied for eight minutes demonstrated that the oxygenated haemoglobin and myoglobin fell progressively to a steady state after six minutes and the deoxygenated haemoglobin and myoglobin showed a reciprocal response (Hampson and Piantadosi, 1988). There was little change, as expected, in the blood volume. On release of the tourniquet, the blood volume rose and corresponded with a rapid increase in oxygenated haemoglobin and myoglobin that continued above the resting level for a further seven minutes before returning to normal. Reciprocal changes were again seen with the deoxygenated haemoglobin and myoglobin. This response after release of the tourniquet is commonly referred to as the 'hyperaemic response'. In contrast, venous occlusion of the arm at 50 mmHg demonstrated a steady rise in blood volume accompanied by a rise in deoxygenated haemoglobin and myoglobin. The oxygenated haemoglobin and myoglobin remained steady indicating the continued arterial input. These studies indicated the ability of NIRS to detect physiological changes rapidly both in blood volume and tissue oxygen status.

Before reaching the muscle compartments, near-infrared light travels through skin and adipose tissue layers. Un-pigmented skin is believed not to contribute to the NIRS signal. Mancini *et al.,* (1994) recorded increased skin blood flow in response to heat without changes in the oxygenated haemoglobin and myglobin signal from NIRS at the same site. Similarly during tourniquet ischaemia, NIRS showed no changes when applied to a double fold of skin and there was poor correlation with transcutaneous pO_2 measurements, suggesting that NIRS measure primarily muscle oxygenation rather than skin (Hampson and Piantadosi, 1988). The effect of hair and skin pigmentation on NIRS has been studied in large animals in both transmission and reflectance mode NIRS (Pringle *et al.,* 1999). To investigate cerebral oxygenation, animals with an average head

width of 14 cm were used. This distance was too great for any transmitted NIRS. Reflectance NIRS with an interoptode distance of 4 cm was possible through white hair and skin. NIRS was not possible through black hair and black skin combined, but was successful once the surface black hair had been removed by shaving. The reason for the black hair effect is unclear, but skin pigmentation due to melanin does not influence NIRS as the wavelength for absorption is below 650 nm. With reference to potential clinical applications in the newborn and liver transplantation patients, the effect of jaundice on NIRS has been investigated. The metabolic breakdown products of the haem molecule that are deposited in the skin absorb near infrared light at the same wavelengths as the parent molecule. Madsen and co-authors (1999) have demonstrated a negative correlation between the cerebral oxygen saturation measured by NIRS and the plasma bilirubin level in jaundiced patients undergoing liver transplantation. This indicates that measurements made by NIRS in trauma patients could be influenced by the presence of haematoma breakdown products in the tissues.

De Blasi (1994), after studying forearm blood flow using NIRS, reported that overweight subjects were not suitable for the study. Binzoni and co-authors (2000) also found high scatter in experimental data in calf NIRS measurements. Both papers suggest that the variability was due to inter-individual physiological differences, namely the range in adipose tissue thickness. It is believed that a greater depth in adipose tissue increases the signal to noise ratio of the NIRS signal. This reduces the linearity of the data, making interpretation difficult. The effect of adipose tissue thickness on NIRS in the human forearm has been quantified (Beekvelt *et al.*, 2001). The adipose tissue depth was determined using skinfold thickness with calipers. A correlation between decreasing muscle oxygen consumption and increasing adipose tissue thickness was demonstrated. A difference in muscle oxygen consumption was found between male and female volunteers,

but the difference was accounted for by the variation in adipose tissue thickness between the sexes. In conclusion, a recommendation was made that in future muscle studies using NIRS that a correction factor for the influence of adipose thickness should be incorporated to justify comparison between different groups.

1.2.3 Applications of NIRS

Since the work by Jobsis (1977), the primary application for near infrared spectroscopy has been to determine intracerebral tissue oxygenation non-invasively. NIRS is suitable for the measurement of cerebral oxygenation due to the obvious problems with direct access to the brain, and the relative consistency in depth of surface tissues between subjects. Animal work in newborn piglets has demonstrated a strong correlation between NIRS and arterial oxygen saturation over a wide range of ventilatory conditions (Brun *et al.*, 1997). This correlation has been confirmed in human volunteers in hypoxic conditions (Pollard *et al.*, 1996). When the volunteers changed position and were placed into 20° Trendelenburg and 20° reverse Trendelenburg, the correlation was not as strong. Similarly the correlation was poor in hypocapneic and hypercapneic states. It was concluded that the loss of correlation between NIRS and arterial saturation was due to the change in cerebral blood flow bought about by the conditions. Further animal work in piglets has shown that haemodilution and subsequent alteration in haemoglobin concentration does not change the linear correlation between NIRS and cerebral arterial saturation. A reduction in haemoglobin concentration however, from $11.1 g.dl^{-1}$ to $8.5 g.dl^{-1}$, did significantly alter the slope and intercept, suggesting the need for a correction factor in interpretation of the NIRS signal (Kurth and Uher, 1997). Despite these confounding factors, a clinical study using NIRS continuous monitoring in patients with head injury examined episodes of impaired cerebral perfusion determined by

alterations in cerebral perfusion pressure, middle cerebral artery flow velocity and cortical perfusion (Kirkpatrick *et al.*, 1995). Thirty-eight episodes of impaired perfusion were recorded. NIRS showed correlated changes in 37 episodes (97%), compared to jugular venous saturation that only detected 20 events (53%) and peripheral oxygen saturation that only responded in 8 (21%) events. This result contributed to the evidence suggesting a strong potential for NIRS in tissue saturation monitoring in clinical practice.

In addition to the ability of NIRS to measure cerebral oxygenation levels, NIRS has been used to localise intracranial haematomas (Gopinath *et al.*, 1993). The increased optical density of the haematoma reduces the amount of reflected light. The optodes of the near-infrared spectrometer can then be moved around the skull to identify areas of increased absorbance. In a clinical study of 46 head injured patients, NIRS was able to identify 40 intracranial haematomas that were later confirmed with CT scanning. Following surgical evacuation of the 40 cases, NIRS demonstrated normal absorbance in 36 patients post-operatively; the remaining 4 had had recurrent bleeds. According to the differences in optical density, this study demonstrated that NIRS performed best in its ability to detect epidural haematomas which are most superficial, followed by subdural haematomas and less clearly for intracerebral haematomas that lie deeper in the tissues.

NIRS technology has been applied to the evaluation of haemorrhagic shock and its resuscitation (McKinley *et al.,* 2000). Soft tissue oxygenation was determined over the anterior deltoid muscle and compared to systemic parameters in patients who had severe multiple trauma and underwent resuscitation in the intensive care unit. The mean injury severity score was 27 (Appendix B). This study, although only involving 8 cases, demonstrated a strong correlation between NIRS and the systemic oxygen delivery index (ml $O_2.min^{-1}.m^{-2}$), which provided a clinical standard alongside other systemic parameters

as to the adequacy of resuscitation following haemorrhagic shock. The study concluded with recommendations for multicentre clinical trials.

In order to extend the possible roles for NIRS, some investigators have moved away from skin surface measurements and have attempted intra-abdominal studies. It is possible to use NIRS technology to measure tissue pH due to the changes in absorbance of haemoglobin induced by accumulating hydrogen ions. In a porcine haemorrhagic shock model using 10 animals, bowel wall pH has been estimated using NIRS and standard pH electrodes. There was close correlation between the NIRS and pH electrodes, although significant inter-subject variability occurred, requiring offset correction for the final data analysis (Puyana *et al.,* 1999). NIRS has also been used intra-operatively in liver transplantation to determine hepatic tissue oxygen saturation (Kitai *et al.,* 1993). NIRS was able to detect variations in oxygenation of the graft liver and that the saturation increased with ligation of porto-systemic shunts.

As a result of the ability of NIRS to detect de-oxygenated haemoglobin, this method has been successfully applied to the evaluation of patients with lower limb venous insufficiency (Hosoi *et al.,* 1997). During a treadmill test, lower leg deoxygenated haemoglobin in normal volunteers fell, consistent with an intact calf muscle pump. The patients with known venous insufficiency, however, had rising deoxygenated haemoglobin levels during the test.

A further application using the ability of NIRS to measure muscle oxygenation and forearm blood flow is in the discrimination between patients with mitochondrial myopathies and those with normal muscle (van Beekvelt *et al.,* 1999). This study has demonstrated that patients with a particular mitochondrial myopathy (chronic progressive external opthalmoplegia) have significantly reduced oxygen consumption at rest and during exercise.

These are a number of the published reports of potential applications for NIRS. Some sources of error and data interpretation still require further investigation and many studies require validation with larger clinical trials before the wider applications of NIRS can be fully explored.

1.3 NIRS AND ACUTE COMPARTMENT SYNDROME

1.3.1 Animal Models

Near-infrared spectroscopy and measurements of compartment pressure have been compared in a porcine model of an acute compartment syndrome (Garr *et al.*, 1999). The compartment syndrome model was produced in nine adult pigs by infusion of colloid into the anterior compartment of the leg. Pressure was created by elevation of the bag of fluid. Pressure was recorded from the compartment by two needles and the mean taken. The NIR optodes were placed over the muscle belly. The development of an acute compartment syndrome was indicated by the loss of neuromuscular function of the anterior tibial compartment muscles. This was determined by placing a nerve stimulator adjacent to the common peroneal nerve and observing for loss of dorsiflexion twitch at the ankle joint. The mean pressure for development of an acute compartment syndrome was 43 mmHg (range 27 – 74 mmHg). This occurred between 93 and 290 minutes following initiation of the infusion. The loss of twitch correlated with a fall in soft tissue oxygenation measured by NIRS from mean 86% to mean 20% (range 0 –54%). After the loss of dorsiflexion twitch, a fasciotomy was carried out. Following this, the compartment pressure returned to resting values and the soft tissue oxygenation returned to 75% in less than ten minutes. The NIRS data correlated with both the compartment pressure and perfusion pressure (mean arterial pressure – compartment pressure). No histological analysis to confirm muscle ischaemia was carried out.

This study has been repeated using the same porcine acute compartment syndrome model to determine if the relationship between compartment pressure and NIRS is maintained in the presence of systemic hypovolaemia and hypoxaemia (Arbabi *et al.*, 1999). Hypovolaemia was induced by phlebotomy until 60% of the mean arterial blood

pressure was obtained. Reducing the inspired oxygen fraction to 0.15 produced the required hypoxaemia. This caused the soft tissue oxygen saturation over the anterior tibial compartment to fall from mean 82% (± 4%) to 66% (± 10%). The addition of the acute compartment syndrome then decreased the soft tissue oxygen saturation to 16% (± 12%). This further fall was significant, indicating that NIRS has the potential to detect an acute compartment syndrome even in the presence of hypovolaemic and systemic hypoxic conditions. In comparison to the non-shocked porcine model, loss of ankle dorsiflexion twitch occurred at a lower perfusion pressure in the latter study, demonstrating that directly measuring muscle oxygenation could be more clinically relevant than tissue pressure measurements.

1.3.2 Volunteer Studies

The development of a human model for the investigation into the diagnosis of an acute compartment syndrome has obvious potential dangers. An entirely non-invasive model has been reported from the same centre that carried out the NIRS and acute compartment syndrome animal work referred to above (Gentilello *et al.*, 2001). They applied a large blood pressure cuff to one leg of 15 volunteers and progressively increased the pressure over 135 minutes. They relied on a published relationship between the cuff pressure and tissue pressure to calculate the intra-compartmental pressure. An 'acute compartment syndrome' was defined by the development of neuromuscular dysfunction that was determined by reduction in conduction velocity and amplitude between the common peroneal nerve at the fibular head and the belly of the tibialis anterior muscle. Sensory changes in the first web space of the foot were also determined. The mean resting soft tissue oxygenation over the tibialis anterior muscle was 86% (S.D. 4.8). Having been subjected to 15 minutes of a calculated compartment pressure of 71 mmHg, the soft tissue

oxygenation had fallen to 59%. Following 120 minutes of cuff pressure that had increased to 79 mmHg, the soft tissue oxygenation had dropped to 2.7% (S.D. 1.7) in 11 volunteers. This reflects the importance of duration of pressure in the development of neuromuscular ischaemia. Following release of the cuff, the soft tissue oxygenation climbed to a mean value of 89%. During the period of cuff inflation, the action potential amplitude fell by 73%, which returned to within 8% of the resting value within 15 minutes of cuff deflation. Four volunteers did not complete the allotted time course as they were stopped early due to the development of a complete loss of nerve conduction. Statistical analysis revealed a strong correlation between the calculated limb perfusion pressure and the soft tissue oxygenation measured by NIRS. This paper concludes by emphasisng that in order to make a clinical diagnosis of acute compartment syndrome, the effect of additional factors on NIRS such as the mechanical effects of crush injury to muscle, intramuscular haematoma and oedema must be considered.

1.3.3 Clinical Studies

Giannotti and co-authors (2000) have produced the only published report of a clinical study into the potential use of NIRS for the diagnosis of acute compartment syndrome. Nine patients had an acute compartment syndrome in the lower limb following trauma confirmed by clinical and pressure measurements in all four compartments. Absolute compartment pressures were used rather than perfusion pressures. The mean pressure prior to fasciotomy was 64mmHg (± 17mmHg). NIRS recordings were made over the anterior, lateral and superficial posterior compartments. Controls were threefold: first, nine matched controls with lower limb trauma but without signs of acute compartment syndrome, second, measurements from the uninjured leg and third, soft

tissue oxygen measurements made from over the deltoid muscle. The latter groups recorded mean soft tissue oxygenation values of 84% (± 17%) and were not included in the analysis due to the values being too widely spread. The mean soft tissue oxygenation value of the compartment syndrome group was 56% (± 27%) compared to 87% (± 7%) for the matched controls. This was statistically significant. The uninjured legs had a significantly higher mean value of 80% (± 20%) than the compartment syndrome side. However, the sample size was small and therefore may have not been representative of the true population. The compartment syndrome cases all had clear signs of the condition and therefore the ability of NIRS as an early diagnostic tool was not determined. This study found two patients in the compartment syndrome group who had soft tissue oxygenation that was indistinguishable from the matched controls. Three of the compartment syndrome patients also had soft tissue oxygenation values that were no different from the un-injured sides. Conversely, a number of the control patients had soft tissue oxygenation values that were in the 'compartment syndrome' range. No long-term follow up was made to determine if an acute compartment syndrome had been missed in the matched control group. The study demonstrates that a number of variables remain unexplained in the application of NIRS for the diagnosis of an acute compartment syndrome.

1.4 HYPOTHESES AND STRUCTURE OF INVESTIGATION

Measurements obtained non-invasively by near-infrared spectroscopy can reliably detect an acute compartment syndrome.

The animal studies (Garr *et al.*, 1999 and Arbabi *et al.*, 1999) indicated that NIRS is a potential useful tool for the diagnosis of an acute compartment syndrome. The technique performed well in an animal model of acute compartment syndrome. The next step was to carry out a prospective clinical trial to compare the performance of NIRS against an accepted method of acute compartment syndrome diagnosis, namely invasive compartment pressure monitoring. This clinical study comprises the first section of this thesis.

The clinical study suggested two possible significant sources of error that could account for the poorer than expected clinical results. These sources of error were then investigated in turn using an animal model of acute compartment syndrome and a study of the variation of baseline parameters within normal volunteers

2 CLINICAL STUDY

2.1 Introduction

Near-infrared spectroscopy, in an animal model of an acute compartment syndrome has correlated with intracompartmental pressure and altered neuromuscular function (Garr *et al.*, 1999). The only published clinical study demonstrated a statistically significant difference between the compartment syndrome group and matched controls (Giannotti *et al.*, 2000). Criticisms of this study included the need for a larger clinical trial, and in order to assess a potential clinical application, NIRS technology must be compared to current validated standards of acute compartment syndrome diagnosis (McQueen and Court-Brown, 1996).

Previous work has identified the particular patients who are at the greatest risk of developing an acute compartment syndrome among adult patients. (McQueen *et al.*, 2000). For this group of at risk patients, continuous compartment pressure monitoring has the additional advantage of providing trend data to aid the diagnostic process. To investigate the hypothesis, the clinical section of this thesis compares invasive continuous compartment pressure monitoring with non-invasive near-infrared spectroscopic monitoring in a prospective sample of at risk patients admitted following isolated lower or upper limb injury. Data has also been collected using ultrasound measurements to investigate the potential influence of limb swelling on NIRS. The study group underwent follow-up at six months to examine for the presence of a missed diagnosis of acute compartment syndrome.

2.2 Materials and Methods

Ethical approval to carry out the clinical section of this project was sought and granted by the Lothian Research Ethics Committee, Deaconess House, 148, Pleasance, Edinburgh. EH8 9RS (Appendix I).

Investigational device

The Inspectra ™ Tissue Spectrometer (model 325) was provided for use in this study by Hutchinson Technology Incorporated (HTI), Hutchinson, Minnesota, USA.

The Inspectra ™ Tissue Spectrometer consists of three components (Figure 4).

1) The first component is a monitor containing the light detection circuits, microprocessor and a display screen.

2) The second component is the fibreoptic cable assembly that contains one set of optical fibres to transmit light to the tissue and a second set of optical fibres that receives light from the tissue and returns it to the photosensitive detector. Light emitting diodes in the cable assembly connector serve as the light source. The distal end of the cable assembly is placed in a soft foam adhesive pad that attaches to the skin surface and also acts to occlude ambient light.

3) The third component is the calibration block that is used prior to data collection by the spectrometer.

This device uses tissue absorbance values at specific wavelengths between 650 – 900 nm to measure the deoxygenated haemoglobin (Hb) and oxygenated haemoglobin (HbO_2) concentrations. These values are added internally to provide a value for the total haemoglobin (Hbt) in the light pathway. The internal algorithm uses the Hbt value to

adjust the output for total haemoglobin changes. The device displays an output, as a percentage, that is calculated as follows:

$$(HbO_2/(HbO_2 + Hb)) \times 100$$

This value is known as the soft tissue oxygen saturation value - **StO_2** (%)

Methaemoglobin and carboxyhaemoglobin are not included in the calculation of StO_2. If these molecules are present in the blood, it is reported that they may interfere with the StO_2 value (InSpectra^{TM} Tissue Spectrometer. Operators Manual. Hutchinson Technology Incorporated (HTI), Hutchinson, Minnesota, USA. 2000).

StO_2 measurements using the InSpectra^{TM} Tissue Spectrometer have been validated using *in vitro* and isolated perfused tissue experiments. In isolated blood perfused porcine hearts, the haemoglobin oxygen saturation measured by the InSpectra^{TM} Tissue Spectrometer strongly correlated (r^2=0.94) with the mean of the arterial and venous haemoglobin saturations (InSpectra^{TM} Tissue Spectrometer. Operation Manual. Hutchinson Technology Incorporated (HTI), Hutchinson, Minnesota, USA. 2000).

The depth of tissue measured by this device is directly proportional to the distance between the illuminating and receiving fibres (Cui *et al.*, 1991). This is known as the inter-optode distance. In phantom solutions containing scattering and absorbing components proportioned to mimic well perfused tissue, studies of spacing between illumination and detection fibers suggest that with 25 mm spacing, approximately 95% of the detected optical signal is from a depth of zero to 23 mm (Hutchinson Technology, unpublished data, 1997). This is adequate for measurement of the skeletal muscle in the anterior compartment of the lower extremity and the volar compartment of the forearm. During the animal and volunteer studies, instruments that have an inter-optode distance of 12 mm and 35mm were also investigated.

Several features are incorporated in the InSpectra™ Tissue Spectrometer to eliminate possible tissue damage resulting from exposure to excessive optical energy. The 25-watt tungsten halogen light source emits a spectrum ranging from approximately 300 nm to 3800 nm. The InSpectra™ Tissue Spectrometer utilizes a small portion of that spectrum in the range of 500 nm to 1150 nm. The spectrum outside this range is filtered out by two methods. Light in the spectrum below 500 nm is prevented from reaching the patient by a high pass filter. The infrared light above 1150 nm is blocked by a liquid filter. In the unlikely event that the liquid filter fails, a silicon photodetector will interrupt power to the tungsten halogen bulb, inactivating the InSpectra™ Tissue Spectrometer monitoring function.

The InSpectra™ Tissue Spectrometer has been designed with an isolated power supply and plastic case to maximize isolation between the power supply and the operator. The probe is constructed of nonconductive fibreoptic cable to eliminate electrical conduction between the monitor and the patient. The device meets the American National Standard, Safe Current Limits for Electromedical Apparatus established by the Association for the Advancement of Medical Instrumentation and is in compliance with the electromagnetic compatibility immunity requirements defined in European Standard EN 60601-1-2 and electromagnetic compatibility emissions requirements defined in European Standard EN 55011.

The InSpectra™ Tissue Spectrometer (model 325) has market approval from the Food and Drug Agency (USA) as a class II (investigational) device. Local research ethics committee approval was therefore sought before clinical studies were started.

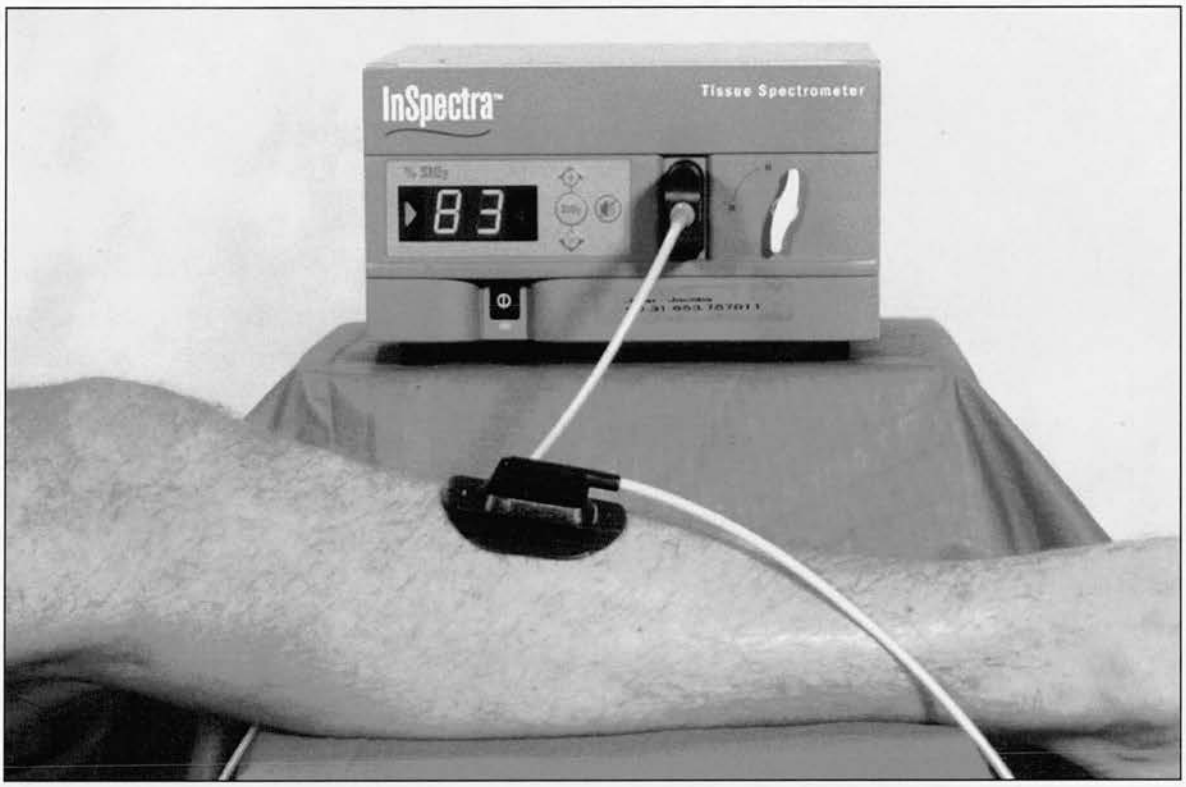

Figure 4 The Inspectra ^{TM} Tissue Spectrometer (Hutchinson Technology Incorporated (HTI), Hutchinson, Minnesota, USA.) Note the single output reading - StO_2 (%)

Subject selection

Recruitment to this study was considered in consecutive patients over the age of 13 years admitted to the Edinburgh Orthopaedic Trauma Unit who were considered to be at risk of acute compartment syndrome. Those patients known to be at risk included patients with tibial diaphyseal fractures and those with high-energy fractures of the forearm diaphysis or distal radius.

Inclusion criteria

1. Male or female patients* with acute fractures of the tibial diaphysis.
2. Male or female patients* with acute high-energy fractures of the forearm diaphysis or distal radius.
3. Male or female patients* with soft tissue injuries of forearms or legs that require invasive pressure monitoring.
4. Patients must have sufficient intact skin over the extremities to accommodate placement of the tissue spectrometer interface. Open fractures were not excluded.

   * *Minimum age = 13.*

Exclusion criteria

1. Patients (or parents/guardian†) unable or unwilling to give informed consent.
2. Major trauma (Injury Severity Score greater than 15, see Appendix B).
3. Chest injury (requiring admission to high dependency unit or intensive care unit).
4. Contralateral limb fracture or soft tissue injury preventing adequate placement of the tissue spectrometer.

   † *patients aged 13-16years*

Inclusion into the study required the fulfilment of the above criteria. Informed consent to take part in the study was obtained and was recorded by signature on the consent form (Appendix C).

Patient and injury data collection

For each patient entered into the study, demographic details were collected and entered into a case report form (Appendix D). The details relating to the history and mechanism of the injury were also noted. For patients sustaining a fracture, the time of admission to the Accident and Emergency Department (A&E), which is printed on the admission sheet, was recorded as the start point. Patients sustaining a fracture reach the orthopaedic ward, via A&E, after a mean delay of 3.7 hours (range 0.5 – 44 hours) following the injury (Hope and McQueen, 2004). Patients who do not have a fracture however, but only limb swelling, present and are admitted to the ward after a delay of more than 24 hours. The time of onset of swelling and the admission time for no fracture patients were therefore also recorded.

The fracture patterns were classified and recorded according to the AO classification (Müller, 1990). Closed fractures were assessed using the Tscherne classification (Oestern and Tscherne, 1984) to determine the degree of soft tissue damage (Appendix E). The open fractures were classified according to the modification of the Gustilo and Anderson classification (Gustilo *et al.*, 1984; Appendix E).

Compartment pressure monitoring

Patients who were recruited to the study underwent continuous invasive compartment pressure monitoring. The forearm or leg plaster backslabs were split to allow invasive and noninvasive monitoring to take place. Invasive pressure monitors were inserted into the anterior compartment of the lower leg or volar forearm of the relevant injured limb. A split 20-gauge jugular venous catheter was used for this purpose (Rorabeck *et al.*, 1981). It was prepared by cutting two slits at the tip prior to insertion into the compartment to be monitored (Figure 5). The catheter is then connected to a

saline filled tube and pressure transducer to allow continuous measurements to be made. This technique can potentially give falsely elevated readings initially if the catheter is flushed over enthusiastically, likewise if the column of saline includes any air, the readings can be damped thus giving false low pressures. Correct technique enables these potential errors to be avoided (Appendix A). The catheter was inserted so that the tip came to lie within 5 cm, proximally or distally, of the fracture site (Heppenstall *et al.*, 1994). Continuous compartment pressure monitoring was carried out from the time of admission to the orthopaedic unit for 24 hours or until a fasciotomy was carried out. If after 24 hours the pressure remained elevated and was not falling, the compartment monitoring was continued. The nursing staff recorded the patient's compartment pressure and blood pressure every hour. A calculation of the ΔP was made hourly by the subtraction of the compartment pressure from the diastolic blood pressure. In addition, clinical findings of impaired active distal limb movement and level of pain were recorded. The evidence of any altered distal limb sensation was also established and detailed on the bedside observation chart.

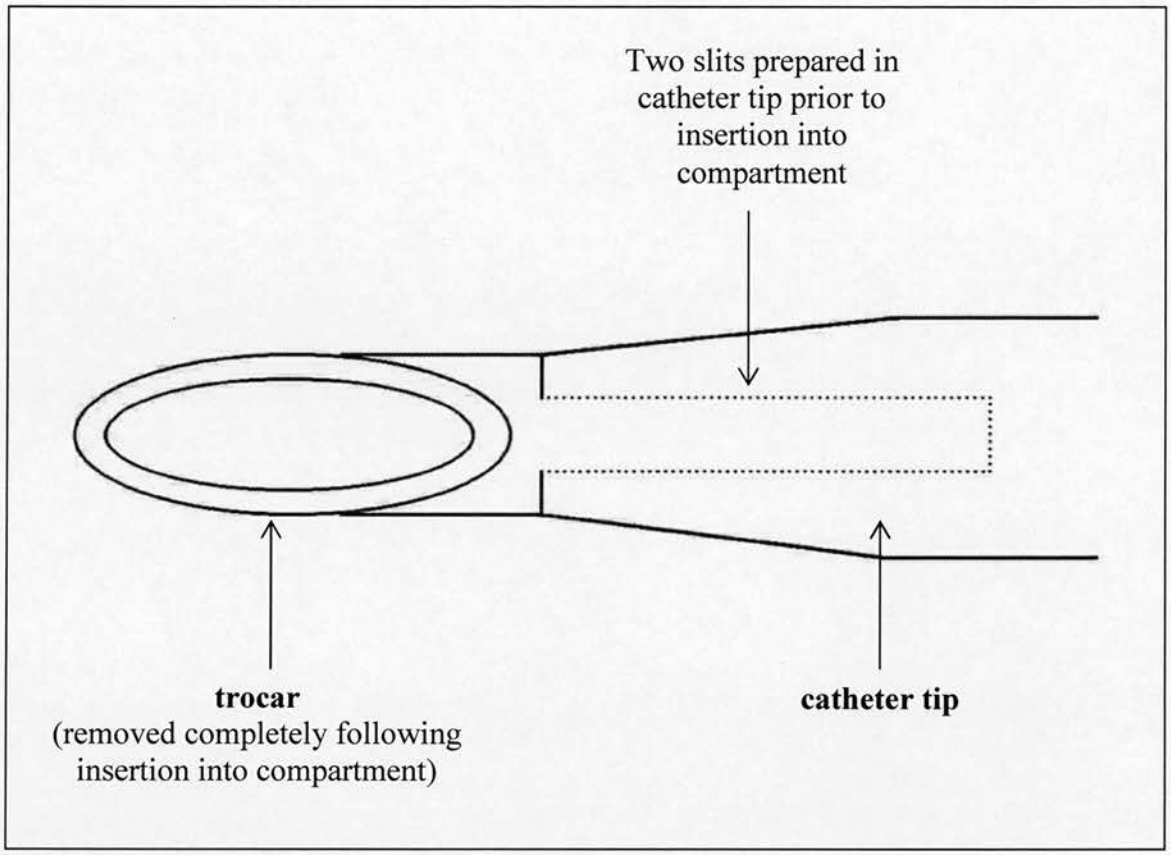

Figure 5 Diagram of slit catheter tip and needle trocar for introduction.

Criteria for surgical decompression

The pressure threshold for decompression used in this study was in accordance with published recommendations (McQueen and Court-Brown, 1996). Decompression was carried out if the ΔP (diastolic blood pressure - compartment pressure) fell and was maintained below 30 mmHg for two hours. The consultant responsible for the clinical care of that patient took the decision with regard to the decompression. The author was not involved in the clinical management of any of the study patients.

Near-infrared non-invasive monitoring.

At the same time as initiating the compartment pressure monitoring, StO_2 measurements were started using the InSpectra^{TM} Tissue Spectrometer. The patient interface was placed on intact skin over the anterior leg or volar forearm compartment. The exact position of the interface on the leg is shown in figure 5. This position has been found to provide a high mean value of STO_2 with a low inter-subject variability in 12 male and 12 female volunteer subjects carried out as a preliminary investigation at the Edinburgh Orthopaedic Trauma Unit (unpublished data, Edinburgh Orthopaedic Trauma Unit, 2000, appendix M). On the forearm, the interface was placed 10 cm distal to the medial epicondyle along a line between the medial epicondyle and the midpoint of the flexor crease at the wrist. Similarly, this was found to be a site with the least variation in StO_2 amongst 10 volunteers (unpublished data, Edinburgh Orthopaedic Trauma Unit, 2000, appendix M). An identical adhesive patch was attached to the individual on the uninjured contralateral side at exactly the same site as that on the injured limb.

At hourly intervals, a recording of the StO_2 measurement from both the injured and the uninjured limbs were made. These recordings were carried out by the nursing staff and documented on the observation charts alongside the pressure recordings. The StO_2

measurements were continued until the invasive compartment pressure monitoring was discontinued. Non-invasive monitoring was not carried out following a fasciotomy as a sterile version of the patient interface for the InSpectra^{TM} was not available.

In order to investigate the possibility of variations in the StO_2 over the length of the anterior compartment of the leg following trauma, measurements of StO_2 were carried out where possible before insertion of the pressure catheter and application of the adhesive mounting for the interface of the spectrometer. Data was collected at 1 cm intervals, parallel to the subcutaneous border of the tibia, beginning at the tibial tuberosity and moving distally to the ankle. This was carried over the injured and uninjured legs (Appendix D. Page 7). These measurements were carried out after recruitment of the first 30 patients to the study in the light of interim analysis of results indicating possible variation in StO_2 measurements with position over the muscle compartment.

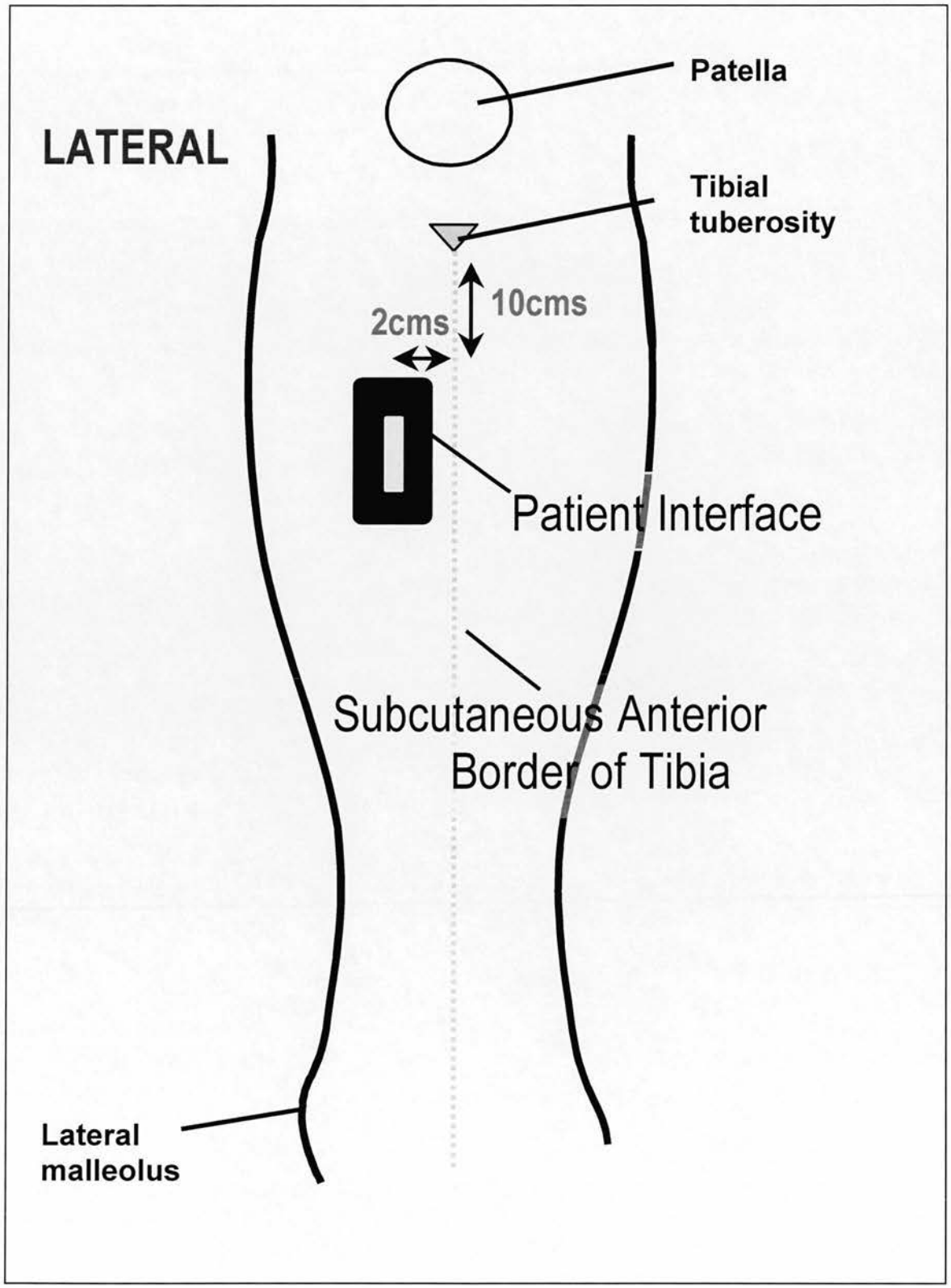

Figure 6 Position of patient interface over anterior compartment of lower leg. The interface is placed 10 cm distal from the tibial tuberosity and 2 cm lateral from the subcutaneous anterior border of the tibia.

Ultrasound

Previous non-clinical studies have indicated that the degree of soft tissue overlying the muscle compartments may influence the ability of near-infrared spectroscopy to determine the tissue oxygenation accurately. Similarly the degree of swelling associated with limb trauma could have an effect on this measurement. In order to investigate this possible source of error, depth measurements were made using a portable ultrasound machine (Sonosite^{TM} 180, Sonosite Inc., Bothel, Washington, USA; supplied by Medical Supplies (UK) Ltd.). The author carried out all ultrasound measurements after initial training by Dr Ian Beggs, Consultant Radiologist, Edinburgh Royal Infirmary. Ultrasound measurements between skin and fascia were carried out on a cadaveric anterior leg at 15 sites prior to dissection to confirm the depth (Department of Anatomy, University of Edinburgh). The mean difference between ultrasound calculated depth and the observed depth, by dissection, was – 0.015 (±SD 0.06)

Ultrasound measurements were only carried out on patients with leg injuries, due to the difficulty in access and discomfort that was likely to be caused for those with arm injuries. The distances between skin and the fascia covering the compartment and the depth of the compartment were recorded. Recordings were made at 5 cms and 10 cms distal to the tibial tuberosity on both the injured and uninjured legs. Ultrasound measurements were carried out immediately prior to the setting up of the compartment pressure and non-invasive monitoring and then either at the completion of the monitoring or prior to a fasciotomy. The availability of the ultrasound also allowed clarification of the positioning of the pressure-monitoring catheter in relation to the fracture (Figure 7).

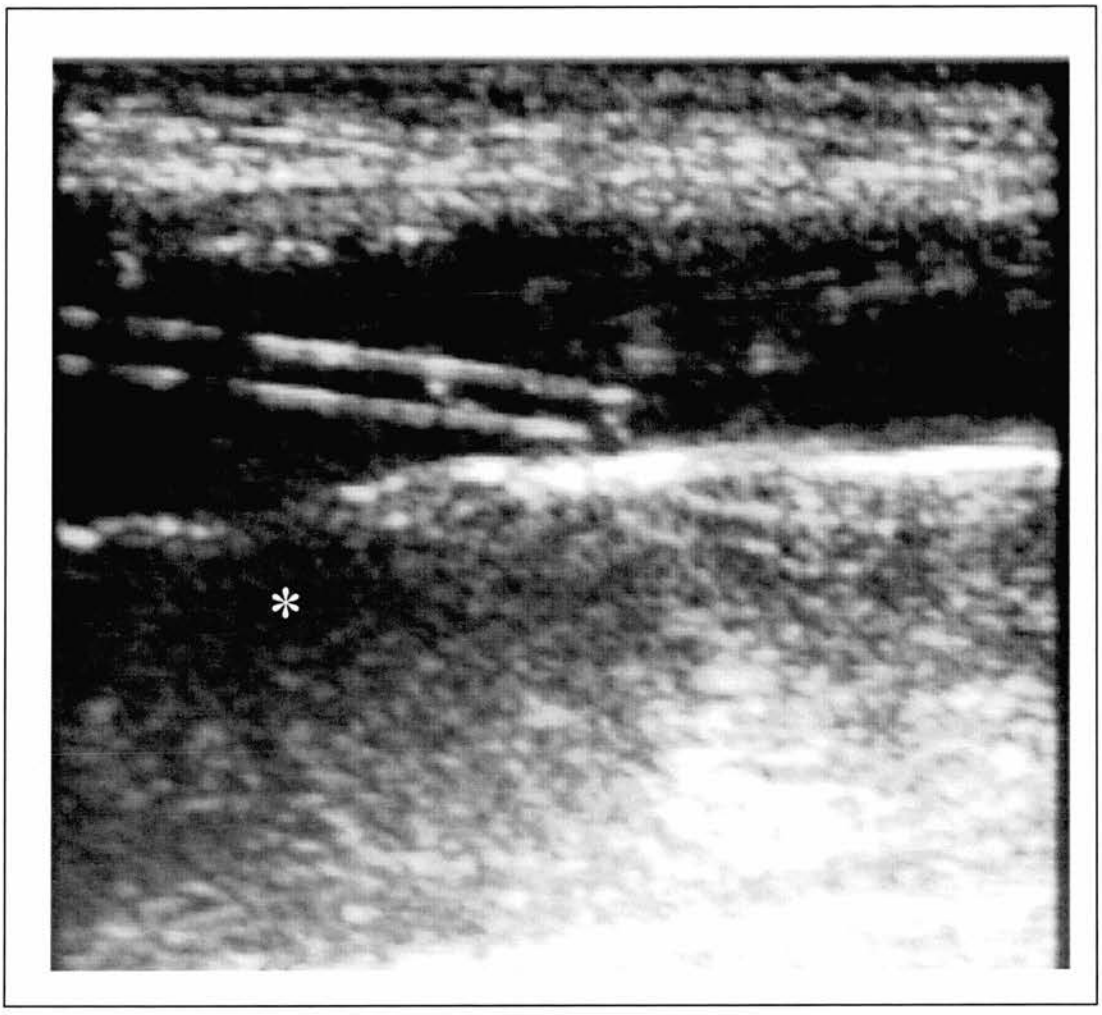

Figure 7 Ultrasound image of compartment pressure catheter alongside a tibial fracture (*)

Analgesia

For the duration of invasive compartment monitoring, the use of analgesia by each patient was recorded. This included intra-venous and intra-muscular opiates and oral opiate analogues. Conversion of the total dosage consumed to an equivalent intra-venous morphine dosage, as a standard was made when the compartment monitoring was completed (Appendix F).

Follow up

Follow up was carried out at the Orthopaedic Outpatients Department of the Edinburgh Orthopaedic Trauma Unit. Patients were seen for regular review by departmental staff, but formal assessment was carried out at 6 months following the injury by the author using a proforma. The purpose of the assessment was to establish if any subjects had sequaelae suggestive of a missed compartment syndrome. The clinical examination looked for evidence of contractures and assessed the power in muscle groups using the MRC standard 5 point scale. Distal limb sensation was recorded as normal, diminished or absent.

Statistical Analysis

Statistical analysis was performed using the multilevel modelling software SPSS (version 14.0, SPSS Inc., Chicago, USA) to assess the linearity of the relationship between ΔP and StO_2. This software allows both measurement-level factors (such as ΔP) and patient-level factors (such as age and sex) to be included. The fit of the appropriate curves allow calibration of the StO_2 values to the invasive compartment monitoring values.

All data are reported as means ± SD. The level of significance was set at $p \leq 0.05$.

2.3 Results

Recruitment to the clinical study took place between January 2000 and January 2002. During the period March 2000 and August 2000, 15 patients had been selected for the study, after which the recruitment was temporarily stopped. This allowed time for assessment of the feasibility of a larger clinical trial and a replacement model of the Inspectra ™ Tissue Spectrometer to be supplied. For the initial period the minimum age for recruitment was 16 years. During the second recruitment period the age for inclusion in the study was lowered to 13 years after further ethical approval was granted from the Lothian Research Ethics Committee. The age range was lowered so that younger adolescent patients who are at high risk of developing an acute compartment syndrome (McQueen *et al.*, 2000) could also be included. To allow the addition of patients younger than 16 years the consent form was devised with alternative wording and space for an adult signature (appendix C)

A total of 102 patients were recruited, 71 males (mean 35 years, range 13 – 88 years) and 32 females (mean 49 years, range 18 – 86 years). Three male patients were recruited who were younger than 16 years. Figure 8 demonstrates the age distribution with respect to fasciotomy and non-fasciotomy cases. The distribution is not normal and is skewed for both fasciotomy and non-fasciotomy cases. During the study period 68 patients were excluded. There were 52 males (mean 35 years, range 13 – 78 years) and 16 females (mean 49 years, range 14 – 92 years). The reasons for exclusion are given in table 4. The rate of fascial decompression in the excluded patients was 15.3%. This compares to 21.6% in the recruited group. This reflects the selected nature of the study patients. The study patients underwent invasive monitoring in priority to some of the excluded patients

where no monitoring was carried out or a second monitor had not been available. This decision was taken on the grounds of injury, fracture and demographic characteristics known to indicate an increased risk for developing an acute compartment syndrome (McQueen *et al.*, 2000). Eight patients did not sign a consent form, two of whom suffered from dementia and the remaining six were less than 16 years, and although could have taken part in the study, chose not to due to parental and patient anxiety with regard to their injury and possible inclusion in a clinical study.

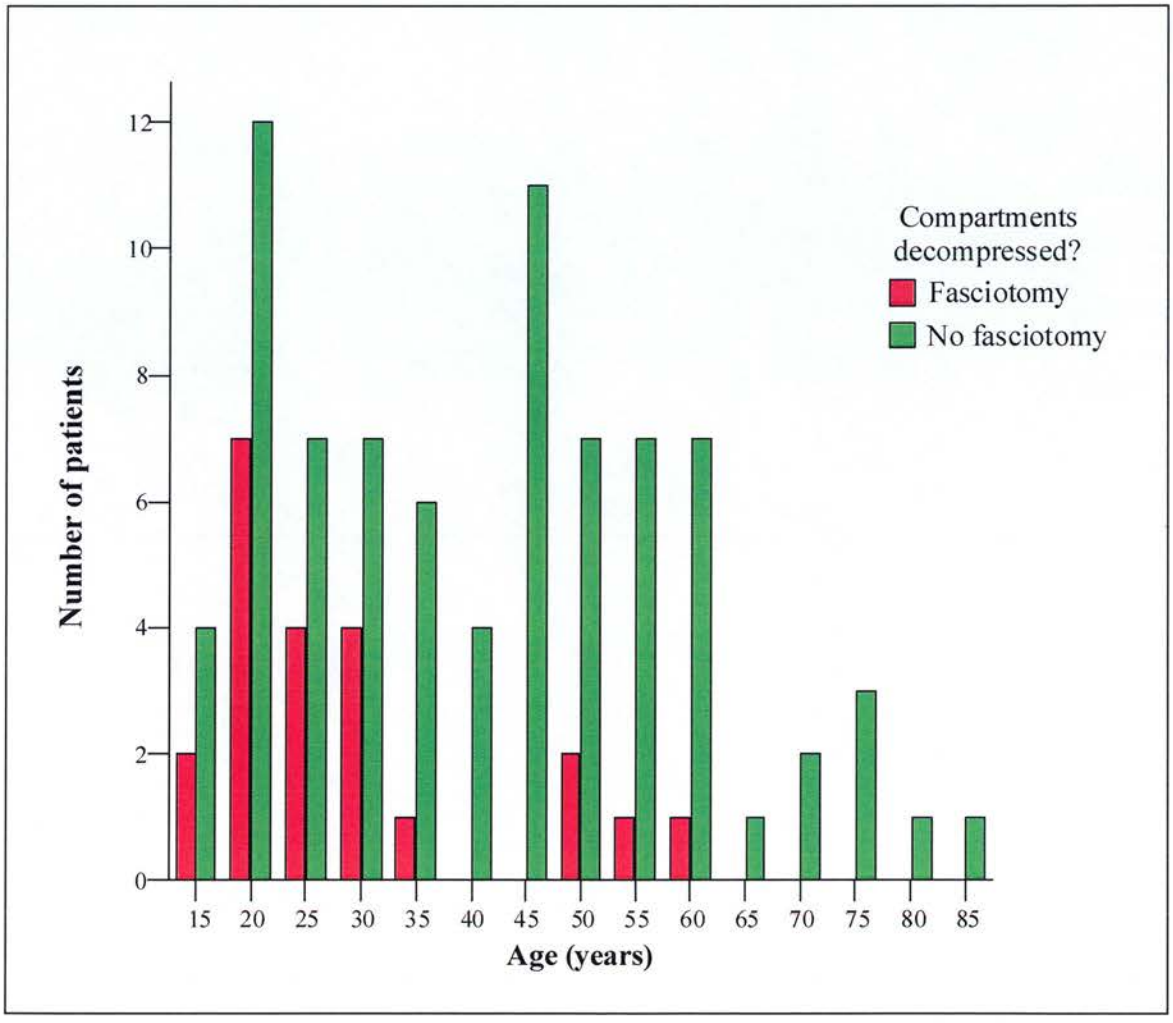

Figure 8 Age distribution of cases and fasciotomies. (Total = 102 cases)

Reason for Exclusion	**Exclusions** Total = 68	
	No decompression 59 cases	**Decompression** 9 cases
author on annual leave	19	1
no continuous invasive pressure monitoring carried out	10	2
multiple injury / ventilated	10	1
second monitored patient	6	2
no signed consent	7	1
not contacted/unable to attend	5	1
insufficient intact skin	2	0
age < 16 years (first part study only)	0	1

Table 4 Reasons for patient exclusion from clinical study.

Injury type, mechanism and fracture classification.

The 102 patients enrolled into the study were divided into 92 tibial shaft fractures, 6 forearm fractures of which four were fractures of the distal radius and ulna. There were four cases were no fracture was sustained; in two the injury involved the thigh and in two the leg. In total, 22 of the 102 patients required compartment decompression. Twenty patients with a tibial shaft fracture and two patients without a fracture were decompressed. The fasciotomy rate in this study cohort was therefore 21.6%. The mean age of patients requiring decompression was 29 years compared to 41 years for the non-fasciotomy patients ($p < 0.001$). The cases undergoing decompression had a sex distribution of 19 male to 3 female ($p = 0.054$).

The mechanisms of injury for the 102 subjects are given in table 5. The types of mechanism are comparable to those reported previously (McQueen and Gaston, 2000). The commonest mechanism was a simple fall, but the mechanism where decompression was most frequent was either an episode of soft tissue swelling without a fracture (50%) or a pedestrian following a road traffic accident where the decompression rate was 45%.

Mechanism of injury	**Number of cases**	**Decompressed (% by mechanism)**
fall from standing height	34	6 (18 %)
fall at sport	17	5 (29 %)
crush injury	14	1 (7 %)
RTA motorcyclist	13	4 (31 %)
RTA pedestrian	11	5 (45 %)
fall down stairs	7	0
fall from height	4	0
Spontaneous/ no fracture	2	1 (50%)
Total	102	22 (22 %)

Table 5 Mechanism of injury and proportions requiring surgical decompression

The classification of soft tissue damage was determined using the Gustilo and Anderson classification for the 11 open fractures (Gustilo *et al.*, 1984) and the Tscherne classification for the remaining 91 closed injuries (Oestern and Tscherne, 1984). The fasciotomy rate for open and closed fractures was 18% and 22% respectively. This difference was not significant, but consistent with published reports which have suggested that high-energy transfer in open injuries may lead to greater internal disruption of

osteofascial boundaries causing a reduction in pressure in otherwise constrained compartments (Rorabeck and McNab, 1976; McQueen *et al.*, 2000). Table 6 shows the soft tissue classifications and number of cases decompressed.

	Tscherne grade	Number of cases	Decompressed
Closed injuries (total = 91)	T 0	42	9 (21%)
	T 1	38	8 (21%)
	T 2	9	2 (22%)
	T 3	2	1 (50%)
	Gustilo and Anderson grade	**Number of cases**	**Decompressed**
Open fractures (total = 11)	G I	3	1
	G II	3	0
	G IIIA	2	1
	G IIIB	3	0
	G IIIC	0	0

Table 6 Soft tissue injury classification of the 102 cases.

The fracture patterns were recorded using the AO classification. Fractures that were of simple type or 2-part (Types A.1, A.2 and A.3) occurred in 65% of leg injuries, compared to 25% and 6% for types B and C. The proportion requiring decompression within types A, B and C was 19%, 29% and 16% respectively. Although the rate of decompression was higher for moderately severe fractures (Type B), this difference was not significant with the number of patients studied (Figure 9). The occurrence of spiral, oblique and transverse configuration of fractures was 30%, 37% and 28% respectively. The proportion of cases requiring decompression was not significantly related to the fracture configuration.

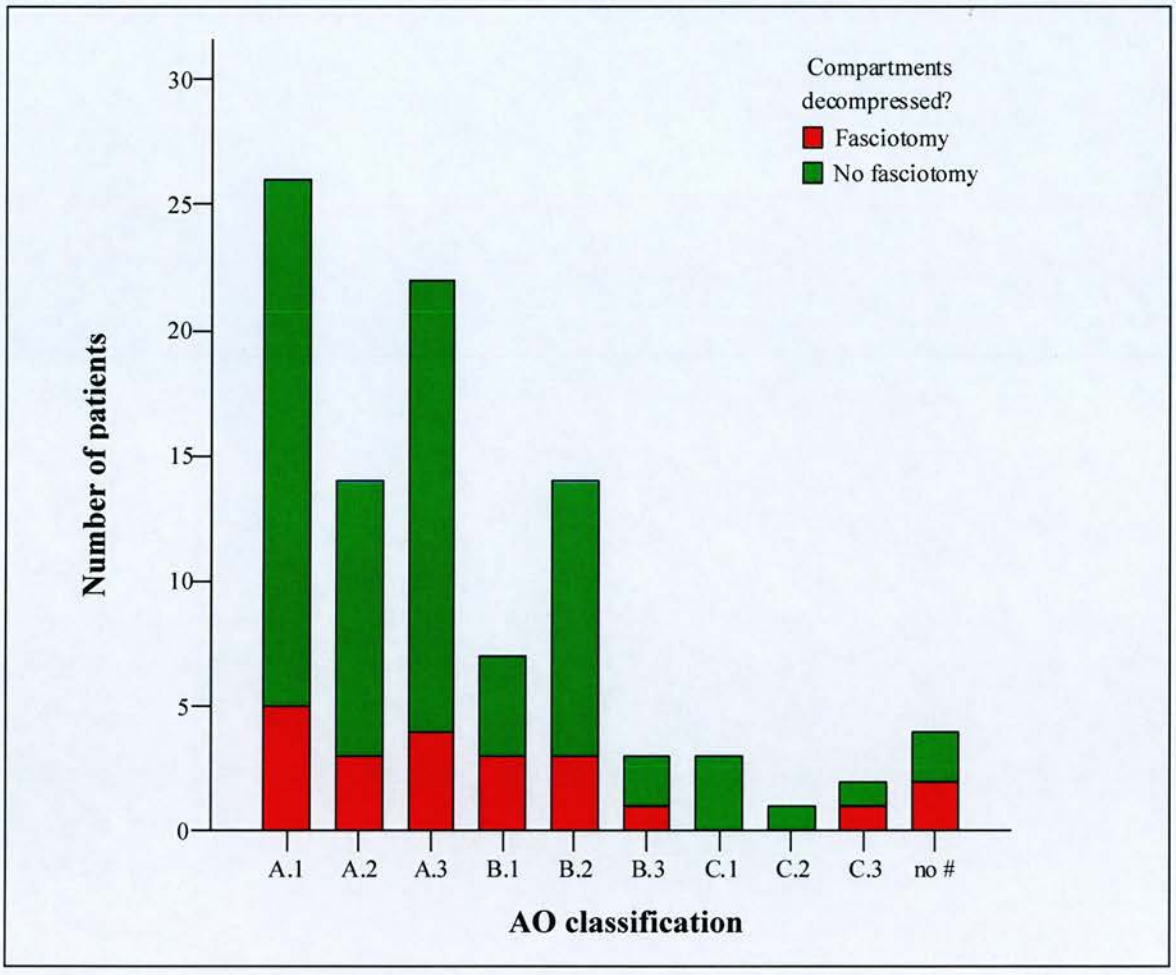

Figure 9 AO classification and decompressions (6 forearm cases not included)

Surgical management

The surgical management of the cases is shown in table 7. This reveals the high proportion of tibial fractures managed by intramedullary nailing. Twenty cases that had sustained a tibial fracture required a fasciotomy. Eighteen of these were managed by intramedullary nailing. The need for surgical decompression was the primary reason for being taken to theatre in 7 of these cases where the nailing and fasciotomy were carried out sequentially, whereas in the other 11 patients the nailing was carried out without complication and then patient required to be returned to theatre for decompression at a later time due to persistently high compartment pressures. The remaining two decompressions had undergone AO plating and external fixation.

	Tibial fractures Total = 92	**Forearm fractures** Total = 6	**Soft tissue injury (no fracture)** Total = 4
Conservative treatment	5	1	2
Internal fixation (intra-medullary nail)	80	0	
Other internal fixation	3	4	
External fixation	4	1	
Surgical decompression	20		2

Table 7 Surgical management of clinical study cases.

Compartment pressure monitoring

Invasive continuous compartment pressure monitoring was carried out in all recruited study patients. For one patient (subject 19) pre-fixation data was not available as the monitoring equipment was being used for other patients. Monitoring equipment became available post-operatively. He did not undergo a fasciotomy. In seven patients it was not possible to complete the total of 24 hours post operative monitoring because the equipment was required by a subsequent patient determined to be at greater risk of developing an acute compartment syndrome (McQueen *et al.*, 2000). In these cases, the second patient was then recruited into the study.

The seven patients that had their injuries managed conservatively had a mean compartment pressure of 17 mmHg (range 7.5 mmHg to 38 mmHg) and a ΔP 55 mmHg (range 36 mmHg to 74 mmHg). On admission to the orthopaedic unit, nine cases were found to have a ΔP of less than 30 mmHg. Six of these patients underwent urgent fasciotomy and definitive fracture treatment. The remaining three cases had definitive surgical treatment and monitoring on the ward for a short period before returning to theatre for a fasciotomy due to a persistent ΔP less than 30 mmHg. One patient (aged 14 years) underwent urgent intra-medullary tibial nailing and fasciotomy; he had a ΔP of 35 mmHg (compartment pressure 49 mmHg), and was decompressed due to his age, fracture and high pressures within three hours of the injury.

The mean compartment pressures and ΔPs for the fasciotomy and non-fasciotomy patients are shown in Table 8. As the decision to carry out a fasciotomy has been based upon the ΔP, the finding of a statistical significant difference is unremarkable.

	Non-fasciotomy		Fasciotomy		Significance
	Mean	SD	Mean	SD	
Compartment Pressure (mmHg)	**22**	**+/- 8**	**48**	**+/- 12**	**$p < 0.001$**
ΔP (mmHg)	**52**	**+/- 10**	**27**	**+/- 13**	**$p < 0.001$**

Table 8 The mean compartment pressures and ΔPs for clinical study cases (Mann-Whitney U test).

Values presented in table 8 are simplified because they do not demonstrate any possible intra-individual and inter-individual variation over time. Patients who have sustained limb trauma and who have been continuously monitored may follow one of four clinical pathways:

Pathway 1 Period of continuous monitoring followed by no surgery or fasciotomy.

Pathway 2 Pre-operative monitoring, definitive fracture fixation followed by further continuous monitoring and no fasciotomy.

Pathway 3 Pre-operative monitoring, definitive fracture fixation followed by further continuous monitoring and later fasciotomy.

Pathway 4 Pre-operative monitoring, followed by fracture fixation and fasciotomy carried out sequentially without returning to the ward.

Continuous compartment pressure monitoring aims to assist the clinician in deciding which course of action to take with regard to carrying out a fasciotomy. Some surgeons, to establish the necessity for a fasciotomy use a single pressure measurement. Analysis of the first recording of ΔP for each subject (Figure 10) reveals a significant difference between the patients who ultimately required a fasciotomy and those who did

not require compartment decompression (38 mmHg and 54 mmHg respectively ($p < 0.001$)). This indicates that either the patients who require a fasciotomy later have a higher resting pressure or that the pathological process leading to an acute compartment syndrome is underway even by the time the first reading has been taken. At the first recording, eight patients had a ΔP less than 30 mmHg; three of these ultimately did not require a fasciotomy as the elevated pressure later settled. Continuous monitoring of the compartment pressure allows discrimination between these cases. Although the difference between the two groups is significant, analysis of the subjects and pressures in relation to the clinical pathway followed provides a clearer picture.

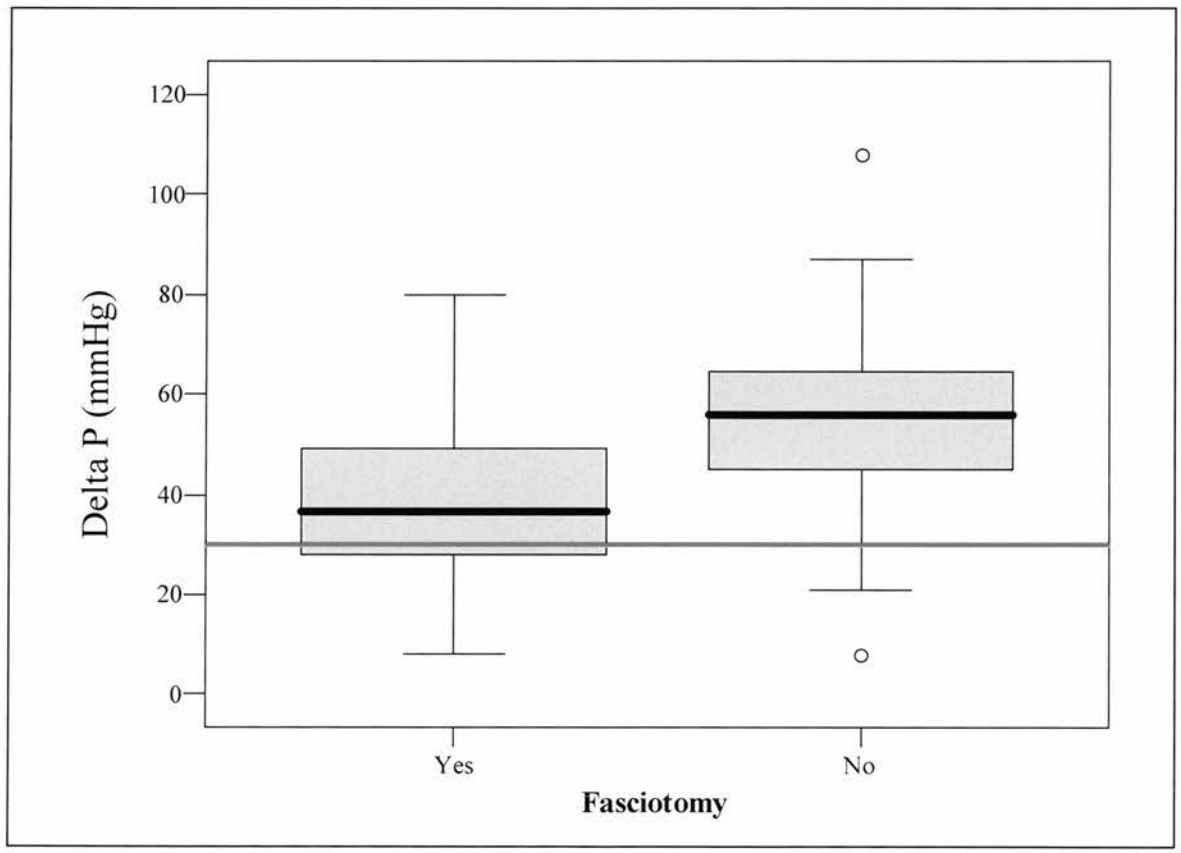

Figure 10 ΔP (mmHg) on admission, grouped according to outcome with regard to fasciotomy.
'Fasciotomy - yes' - mean ΔP = 38 mmHg (SD +/-18 mmHg) and 'Fasciotomy – no' – mean ΔP = 54 mmHg (SD +/-16 mmHg). Red line indicates the threshold for fasciotomy used in this study – $\Delta P \leq 30$ mmHg.

Table 9 shows the mean compartment pressures and ΔP for the four clinical pathways as described above. There was no significant difference in compartment pressures and ΔP between conservatively managed patients and pre-operative values for patients undergoing fixation and not requiring a fasciotomy. There was a highly significant difference ($p < 0.001$) between the *pre-operative* values for the two groups undergoing definitive fixation and subsequent further continuous monitoring on the ward (pathways 2 and 3). Fixation of the fractures, in groups 2 and 3, resulted in a significant change ($p < 0.05$) in compartment pressure and ΔP between the pre- and post fixation values for both groups. The magnitude of this change was greater in group 3, where the pre-operative pressure was already significantly raised, and therefore the post-operative levels were sufficiently high to indicate the need for a fasciotomy according to the threshold criteria of a ΔP less than 30 mmHg.

Clinical pathways	**Number of subjects**	**Pre-fixation (or conservative) mean (+/- SD) compartment pressure and ΔP (mmHg)**	**Post-fixation mean (+/- SD) compartment pressure and ΔP (mmHg)**
1. Conservative	**14**	**21** (± 11) **53** (± 18)	
2. fixation and no fasciotomy	**66**	**19** (± 9) **56** (± 13)	**23** (± 9) **51** (± 11)
3. fixation and later fasciotomy	**13**	**35** (± 19) **37** (± 13)	**54** (± 18) **20** (± 20)
4. urgent fixation with immediate fasciotomy	**9**	**51** (± 7) **27** (± 14)	

Table 9 The mean compartment pressures and ΔPs (mmHg) for subjects by clinical pathways, including pre- and post-fixation mean values for pathways 2 and 3.

Near-infrared non-invasive monitoring.

The non-invasive monitor to determine StO_2 was applied to all subjects in the study according to the methods described above. NIRS monitoring was carried out postoperatively alongside the invasive pressure monitoring for a minimum of 24 hours unless another subject was recruited to the study and deemed to be at greater risk of developing an acute compartment syndrome, in which case the equipment was transferred. Nine subjects had incomplete monitoring either pre or post-fixation as a result of either the monitor on another subject, no signal detection or the author being unavailable to set up the equipment (Table 10). Only one patient had no readings taken from the injured leg during both pre and post-fixation due to no signal detection. The reasons for no signal detection were unclear.

Case No	Pre-fixation	Post-fixation	Fasciotomy	Reason for incomplete monitoring
32	injured side		no	no signal
44	both sides		no	monitor unavailable
52	both sides		yes	author unavailable
55		injured side	yes	no signal
72	both sides		no	monitor unavailable
79		both sides	yes	author unavailable
86		both sides	no	author unavailable
89	both sides		no	monitor unavailable
91	both sides		yes	monitor unavailable
94	injured side	injured side	no	no signal

Table 10 Details and reasons for periods of absent non-invasive monitoring

StO_2 values were recorded from the uninjured and injured sides at the same site over the tibialis anterior or forearm flexor compartment (Figure 6). It was found that the range of values from the uninjured side varied to an extent greater than that which had been predicted from the preliminary work carried out in the Edinburgh Trauma Unit prior to the initiation of the study (Figure 11). To accommodate for this variation, the difference between the uninjured and the injured limb was calculated for every StO_2 recording in each subject. This value has been termed the '**StO_2 difference**'.

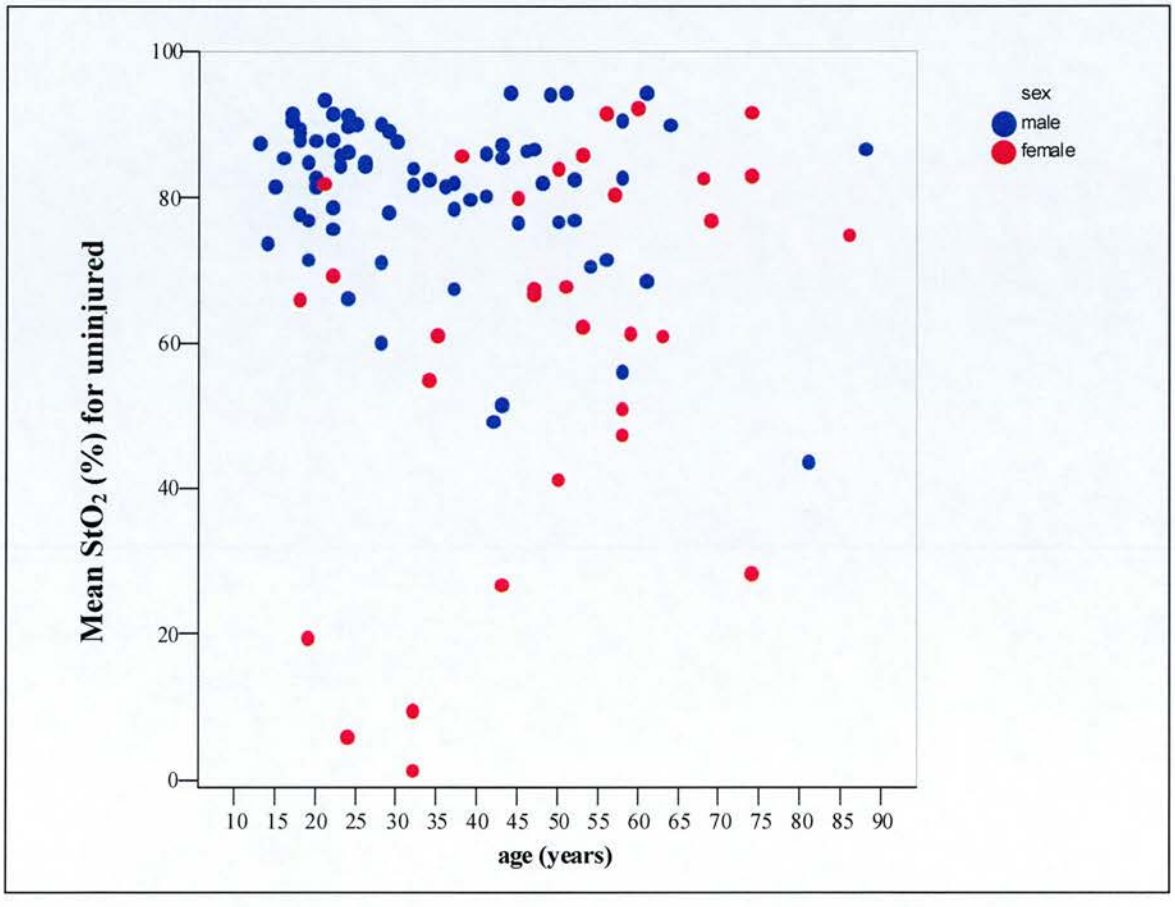

Figure 11 Mean StO_2 (%) for uninjured limbs by age and sex, displaying the wide variation of values. No significant correlation found between age and mean StO_2 for uninjured limbs.

	StO_2 (%) injured limb		**StO_2 (%) uninjured limb**		**Mean difference (%)**	Significance*
	Mean	SD	Mean	SD		
Non-fasciotomy n = 79	**84**	**± 11**	**73**	**± 21**	**10.8**	$p < 0.001$
Fasciotomy n = 21	**80**	**± 14**	**81**	**± 10**	**-1.6**	$p = 0.57$
Significance	$p = 0.3$		$p = 0.1$			

Table 11 StO_2 (%) values comparing each limb and by fasciotomy for clinical study cases (*Paired samples test, Mann-Whitney U test).

Comparison of the mean values of StO_2 for the injured and uninjured limbs in patients who did not require a fasciotomy reveals a significant increase in StO_2 levels on the injured side (Table 11). This finding is in contrast to that of the subjects who underwent a fasciotomy where the StO_2 on the injured side was not elevated above that of the uninjured side. In addition to allowing for variation between patients with regard to the StO_2 values of the uninjured limbs, calculation of the 'StO_2 difference' potentially provides an indication of the relative oxygenation of each limb. The mean 'StO_2 difference' values for the non-fasciotomy cases were significantly raised ($p < 0.001$) compared to fasciotomy cases, the figures being 11% and – 2% respectively. This indicates that a patient who has or is developing an acute compartment syndrome demonstrates a reduction in the StO_2 on the injured side from the elevated measurement that would be expected in an uncomplicated injured limb. No significant difference was seen when the injured sides of fasciotomy and non-fasciotomy patients were compared alone and likewise, no difference was found when the uninjured sides were compared.

Analysis of the StO_2 values with regard to the clinical pathways (Table 12), demonstrates that all patients not requiring a fasciotomy had a mean StO_2 difference of 10% or greater.

Clinical pathways	Number of subjects	Pre-fixation (or conservative) mean StO_2 (%)(± SD)			Post-fixation mean StO_2 (%) (± SD)		
		Injured	Normal	StO_2 Diff.	Injured	Normal	StO_2 Diff.
1. Conservative	**14**	**86** (± 10)	**74** (± 24)	**12** (± 15)			
2. Fixation and no fasciotomy	**52**	**84** (± 13)	**74** (21±)	**10** (± 15)	**83** (±12)	**71** (±22)	**12** (±16)
3. Fixation and later fasciotomy	**10**	**87** (± 6)	**85** (± 7)	**2** (± 10)	**78** (±19)	**84** (± 9)	**-4** (±26)
4. Urgent fixation with immediate fasciotomy	**8**	**77** (± 18)	**78** (± 12)	**-1** (13±)			

Table 12 The mean StO_2 (%) values for subjects by clinical pathways, including pre- and post-fixation mean values for pathways 2 and 3.

There was no statistically significant difference between values for the patients in groups 1 and 2. Reduction and fixation of the fractures did not cause a significant change in the StO_2 values for patients of groups 2 and 3. The magnitude of the changes (in StO_2 difference) was a rise of 2% in the fixation/no fasciotomy group compared to –6% for patients requiring fixation and later fasciotomy. This relative fall in StO_2 for group 3 subjects may represent increasing ischaemia, but the numbers have been insufficient to reach statistical significance. The finding of a low 'StO_2 difference' in the patients in groups 3 and 4 reflects that found in measurements of their ΔP and compartment

pressures. The lowest mean 'StO_2 difference' and lowest ΔP were both found in the post-fixation patients (group 3) prior to fasciotomy, where the mean 'StO_2 difference' was negative reflecting a significant reduction in the StO_2 of the injured limb compared to the non-fasciotomy patients ($p < 0.001$).

Comparison of compartment pressure and StO_2 measurements.

The development of an acute compartment syndrome is believed to be due to a progressive rise in compartment pressure resulting in increasing ischaemia in the tissues. In order to determine if a relationship between compartment pressure and StO_2 exists then any correlation must be examined independently of patient outcome with regard to clinical pathway.

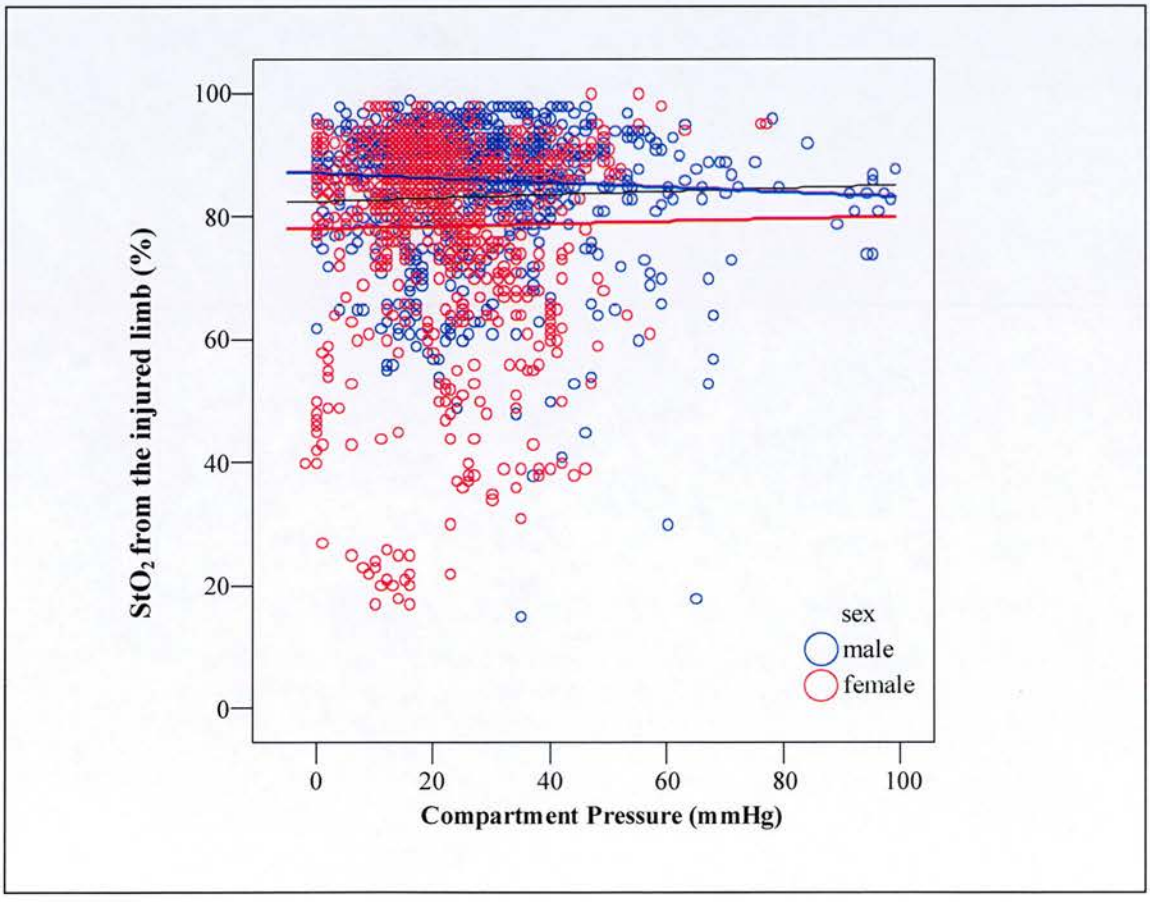

Figure 12 StO_2 from the injured limb (%) and compartment pressure (mmHg) for all subjects, shown by gender. Correlation (Spearman's rho) for all subjects – black line r = 0.01 (p = 0.53); for males – blue line r = -0.02 (p = 0.60); for females – red line = -0.06 (p = 0.1).

When the entire study population of 102 subjects is analysed, StO_2 on the injured limb does not display a significant linear correlation with the compartment pressure (Table 13, Figure 12). When the population is subdivided by sex and fasciotomy, again no significant correlation with StO_2 on the injured limb was observed. A significant correlation was found, however, between the StO_2 on the uninjured limb and the compartment pressure on the injured side. This may reflect that the StO_2 on the uninjured limb was higher in individuals with less adipose tissue that are predominantly found in younger individuals who in turn, are at greater risk of elevated compartment pressures (McQueen *et al.*, 2000). When the 'StO_2 difference' was compared with compartment pressure, a significant negative correlation was observed, indicating that as the pressure increases, the StO_2 value on the injured limb falls with respect to the uninjured side. Calculating ΔP and comparing this to the injured side StO_2 value, reveals a statistically significant correlation for all subjects. Patients who underwent a fasciotomy do not show a correlation between the ΔP and the injured side StO_2. However, by comparing the 'StO_2 difference' and ΔP (Table 13, Figure 13), which reduces inter-patient variability, a statistically significant correlation is seen. By examining the sub-groups, the male fasciotomy patients demonstrate a stronger positive correlation using StO_2 difference, indicating a lowering of the injured limb StO_2 in relation the uninjured side as the ΔP falls (Figure 14).

Correlation	Sub-groups (number of subjects)	Correlation Coefficient	Significance
StO_2 injured (%) and Compartment pressure (mmHg)	All subjects (102)	0.01	0.53
	Male (70)	-0.02	0.60
	Female (32)	-0.06	0.10
	Fasciotomy (22)	-0.15	0.02
	No fasciotomy (80)	0.04	0.08
StO_2 uninjured (%) and Compartment pressure from injured limb (mmHg)	All subjects (102)	0.14	<0.01**
	Male (70)	0.08	<0.01**
	Female (32)	0.06	0.07
	Fasciotomy (22)	0.05	0.42
	No fasciotomy (80)	0.09	<0.01**
'StO_2 difference' (%) and Compartment pressure (mmHg)	All subjects (102)	-0.13	<0.01**
	Male (70)	-0.12	<0.01**
	Female (32)	-0.05	0.19
	Fasciotomy (22)	-0.17	<0.01**
	No fasciotomy (80)	-0.04	0.09
StO_2 injured (%) and ΔP (mmHg)	All subjects (102)	0.06	<0.01**
	Male (70)	-0.01	0.81
	Female (32)	0.18	<0.01**
	Fasciotomy (22)	0.15	0.02
	No fasciotomy (80)	0.05	<0.03*
StO_2 uninjured (%) and ΔP from injured limb (mmHg)	All subjects (102)	-0.06	<0.01**
	Male (70)	-0.10	<0.01**
	Female (32)	0.06	0.12
	Fasciotomy (22)	-0.10	0.13
	No fasciotomy (80)	0.01	0.90
'StO_2 difference' (%) and ΔP (mmHg)	All subjects (102)	0.10	<0.01**
	Male (70)	0.14	<0.01**
	Female (32)	0.02	0.90
	Fasciotomy (22)	0.17	<0.01**
	No fasciotomy (80)	0.01	0.83

Table 13 Comparison of StO_2 values (injured, uninjured and difference) and compartment and Δ pressures. Correlation (Spearman's rho) and significance (* $p < 0.05$, ** $p < 0.01$).

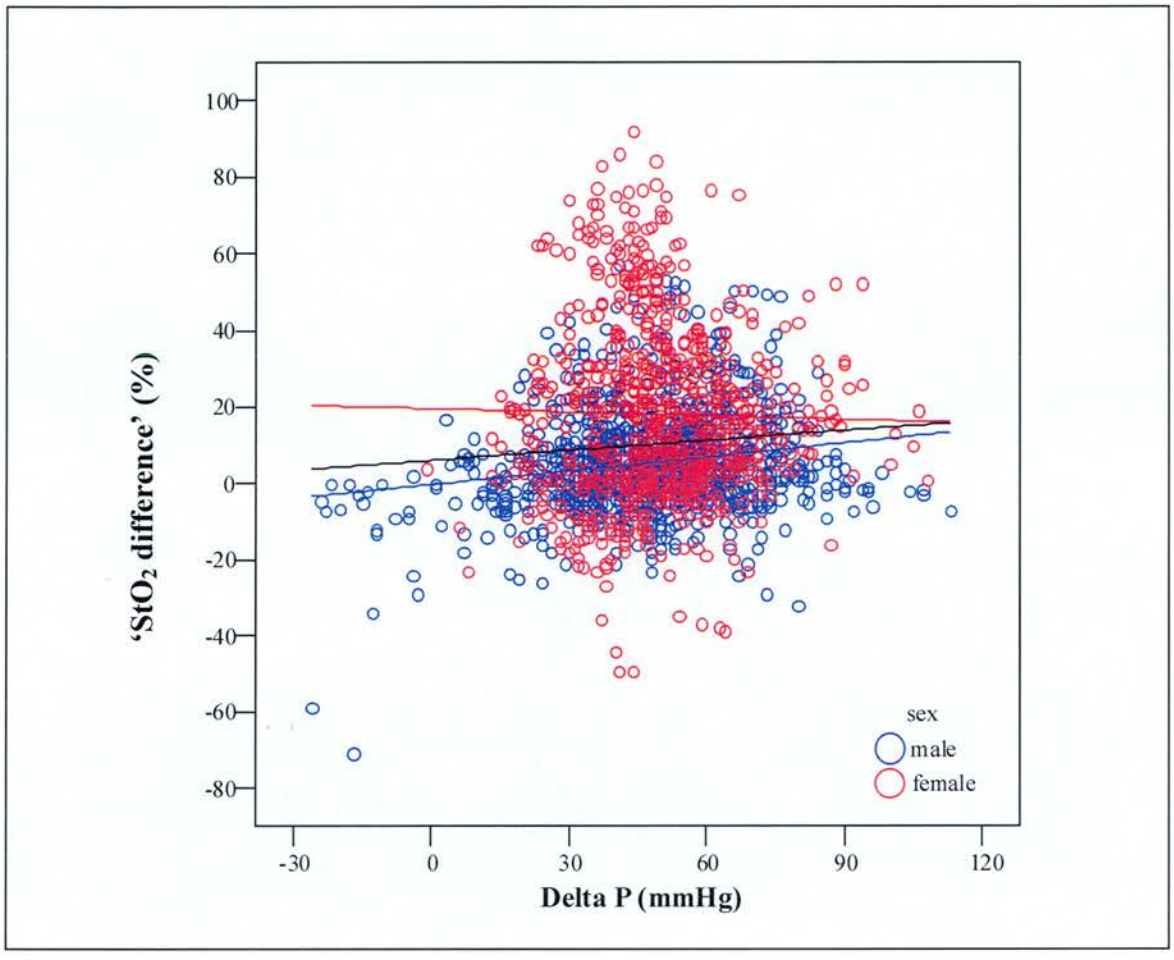

Figure 13 'StO_2 difference' (%) and ΔP (mmHg) for all clinical study subjects. Correlation (Spearman's rho) for all subjects – black line = 0.1 ($p < 0.01$); for all females – red line = - 0.02 ($p = 0.96$); for all males = 0.14 ($p < 0.01$)

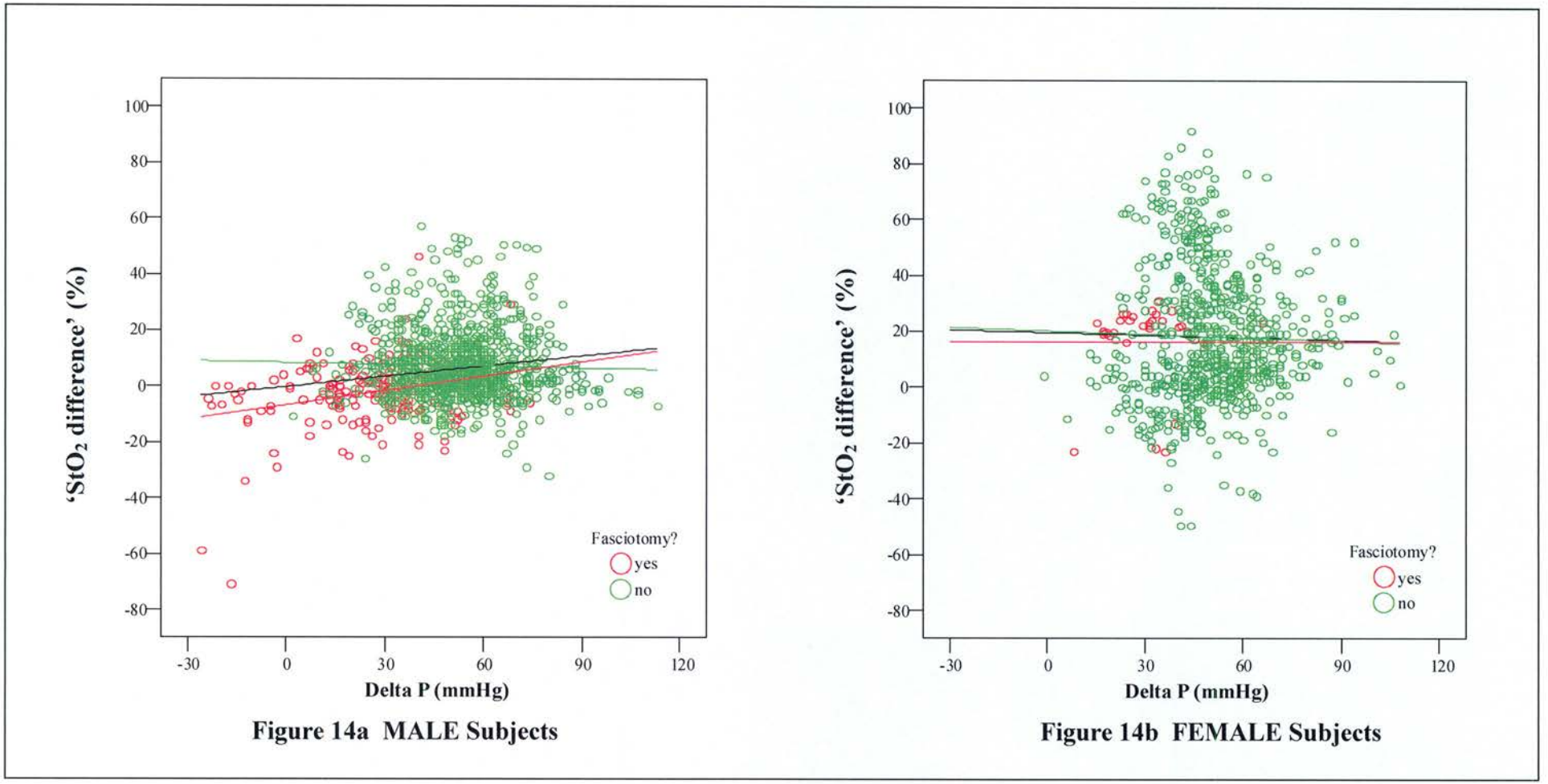

Figure 14a MALE Subjects

Figure 14b FEMALE Subjects

Figure 14 'StO$_2$ difference' (%) and ΔP (mmHg) for male and female subjects, shown by fasciotomy. Correlations (Spearman's rho) for all male subjects (Fig 13a) – black line = 0.002 (p = 0.96); for male patients who had a fasciotomy – red line = 0.014 (p = 0.72); for male patients who did not have a fasciotomy – green line = -0.14 (p =0.42). Correlations (Spearman's rho) for all females (Fig 13b) – black line = 0.14 (p < 0.01); for female patients who had a fasciotomy – red line = 0.19 (p = <0.01); for female patients who did not have a fasciotomy – green line = -0.11 (p = 0.7).

These comparisons have revealed that there was a statistically significant correlation between measurements of soft tissue oxygenation, StO_2, represented by the calculation of the StO_2 difference between the limbs, and the compartment pressure represented by calculating ΔP (diastolic blood pressure minus compartment pressure). It has been found, however, that StO_2 does not correlate with compartment pressure in the subgroups of the study, and that considerable inter-subject variation exists. A high degree of variation in StO_2 measurements has been seen particularly in female subjects and in male patients who did not undergo a fasciotomy (Figure 14). The closest correlation was found in the fasciotomy group in males.

Analgesia

The analgesia used by each subject was converted to the equivalent dose of intravenous morphine (Appendix F). The total duration of the invasive compartment monitoring was calculated for each patient. It is recognised that patients developing a compartment syndrome may experience pain out of proportion to the injury that has been sustained. Pain can be controlled by opiates and therefore the assessment of pain itself may be difficult. The use of opiates, without pressure monitoring, can mask an acute compartment syndrome (Harrington *et al.*, 2000). An awareness of increasing opiate usage may provide an additional indicator of a developing compartment syndrome. The mean total use of opiates for the fasciotomy and non-fasciotomy groups were 62 mg (±SD 103) and 40 mg (±SD 39) respectively. This difference was not significant. The mean duration of monitoring for the fasciotomy group is 12 hours (±SD 11) and 34 hours (±SD 16) for the non-fasciotomy group. It is possible, therefore, to calculate 'opiates used per hour' for comparative purposes. For patients with tibial fractures prior to a fasciotomy, the mean was 12 mg (±SD 32) 'opiate per hour' and for non-fasciotomy patients this was a mean of 1 mg (±SD 1) 'opiate per hour' for the duration of monitoring ($p < 0.01$).

Operative findings

From the study group there were 22 surgical decompressions. Two of these were evacuations of thigh haematomas and the remaining 20 patients had four compartment lower leg decompressions. At the time of surgery an assessment was made of the muscle viability by the operating surgeon. This assessment was made at the beginning and end of the procedure. The muscle was examined for evidence of colour change (Figure 15), ability to bleed when incised and the ability to contract with mechanical stimulation. At the end of the decompression, if the muscle showed signs of doubtful viability this was recorded. Fifteen patients had healthy muscle by the end of the fasciotomy, the remaining five still had signs of doubtful muscle viability. Muscle excision was not carried out at the primary procedure as wound review was carried out 48 hours later. No significant difference was found between the two groups for the mean pre-operative values for compartment pressure, delta pressure, StO_2 uninjured, StO_2 injured, StO_2 difference, and opiate use per hour (table 14).

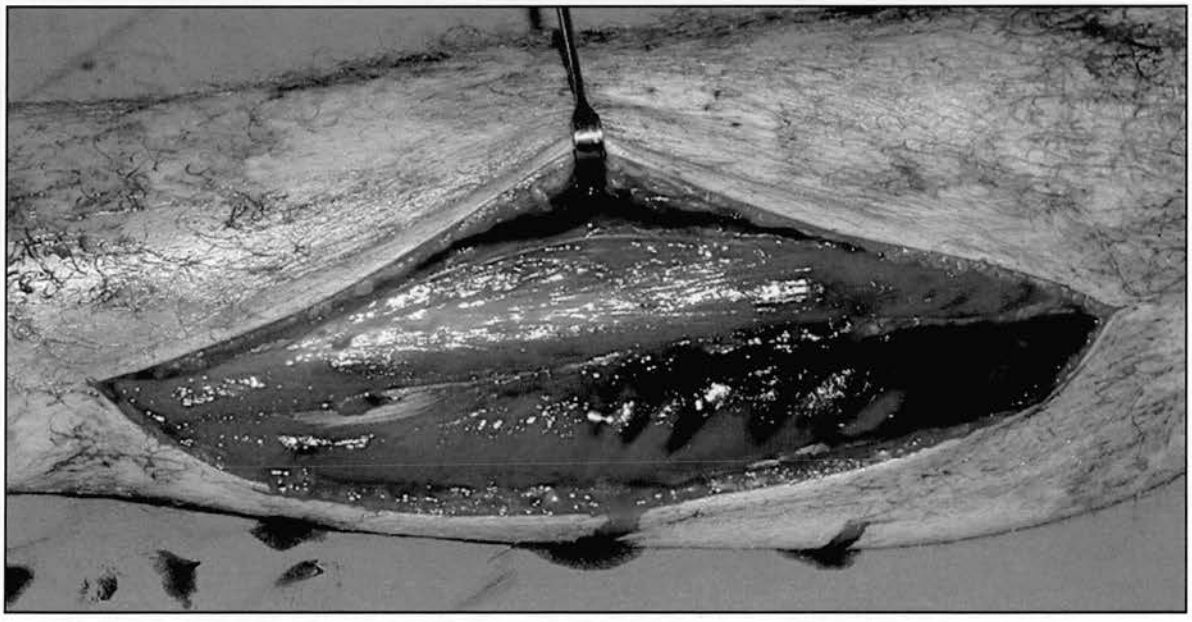

Figure 15 Lateral fasciotomy wound of leg. Striated muscle discolouration can be seen in proximal lateral compartment. These changes had completely resolved by the end of the procedure.

	Viable muscle (n = 15)	**Persistent ischaemic muscle changes** (at end of procedure) **(n = 5)**	**Significance** (p value)
Compartment pressure (mmHg) (± SD)	47 (±14)	50 (±10)	0.6
DeltaP (mmHg) (± SD)	26 (±13)	27 (±15)	0.9
StO_2 uninjured legs (%) (± SD)	85 (±7)	73 (±12)	0.01*
StO_2 injured legs (%) (± SD)	82 (±12)	80 (±11)	0.7
StO_2 difference (%) (± SD)	-2 (±18)	6 (±10)	0.3
Opiates used per hour (mg) (± SD)	3 (±3)	36 (±60)	0.04*

Table 14 Pre-operative mean values for compartment pressure, delta pressure, StO_2 uninjured, StO_2 injured, StO_2 difference, and opiate use per hour (including SD) for the 20 tibial fracture patients who underwent fasciotomy. Grouped by muscle viability at end of fasciotomy procedure.

Longitudinal NIRS recordings

Non-invasive recordings of StO_2 were carried out over the anterior tibial compartment from proximal to distal just prior to the insertion of the invasive pressure-monitoring catheter. These recordings were possible in 70 subjects, 17 of whom later had a fasciotomy. In 29 of the patients it was not possible to obtain a full set of readings down the injured leg as the non-invasive monitor was 'unable to detect a signal' at some of the sites. From this group of 29 patients, there were 6 fasciotomies, which was not statistically different from the 11 fasciotomies where all recordings were possible. The mean time from admission to insertion of the catheter was 5 hours (±2.9 hours). Figure 16

demonstrates StO_2 measurements with progression distally from the tibial tuberosity. Recordings were made at 1 cm intervals and 2 cm lateral to the sub-cutaneous border of the tibia. On the injured leg, there was no significant difference in the StO_2 measurements over the tibialis anterior muscle at the time of catheter insertion when compared to later requirement for decompression (Figure 16a). This was not seen in the un-injured leg where there was a mean difference in StO_2 value of 10% greater in cases that later required a fasciotomy ($p<0.01$, paired samples t-test). When the results are divided by sex rather than fasciotomy, differences in StO_2 measurements are again apparent (Figures 17 - 19). Males have a mean StO_2 7.3% greater ($p<0.01$, paired samples T-test) than females over the length of the injured leg (figure 16a). On the un-injured leg the mean difference was found to be 26% ($p<0.01$, paired samples T-test) lower in female patients. Figure 18 shows that the greatest range of StO_2 values were also found in female patients.

The measurement of StO_2 at intervals along the anterior compartment demonstrates that injured legs maintain a steady StO_2 from proximal to distal (mean decrease of 4%, $n=29$, $p=0.09$, SD±13.3). Values from the un-injured legs, however, demonstrated a fall in StO_2 from proximal to distal of 17% ($n=49$, $p<0.01$, SD±22.2).

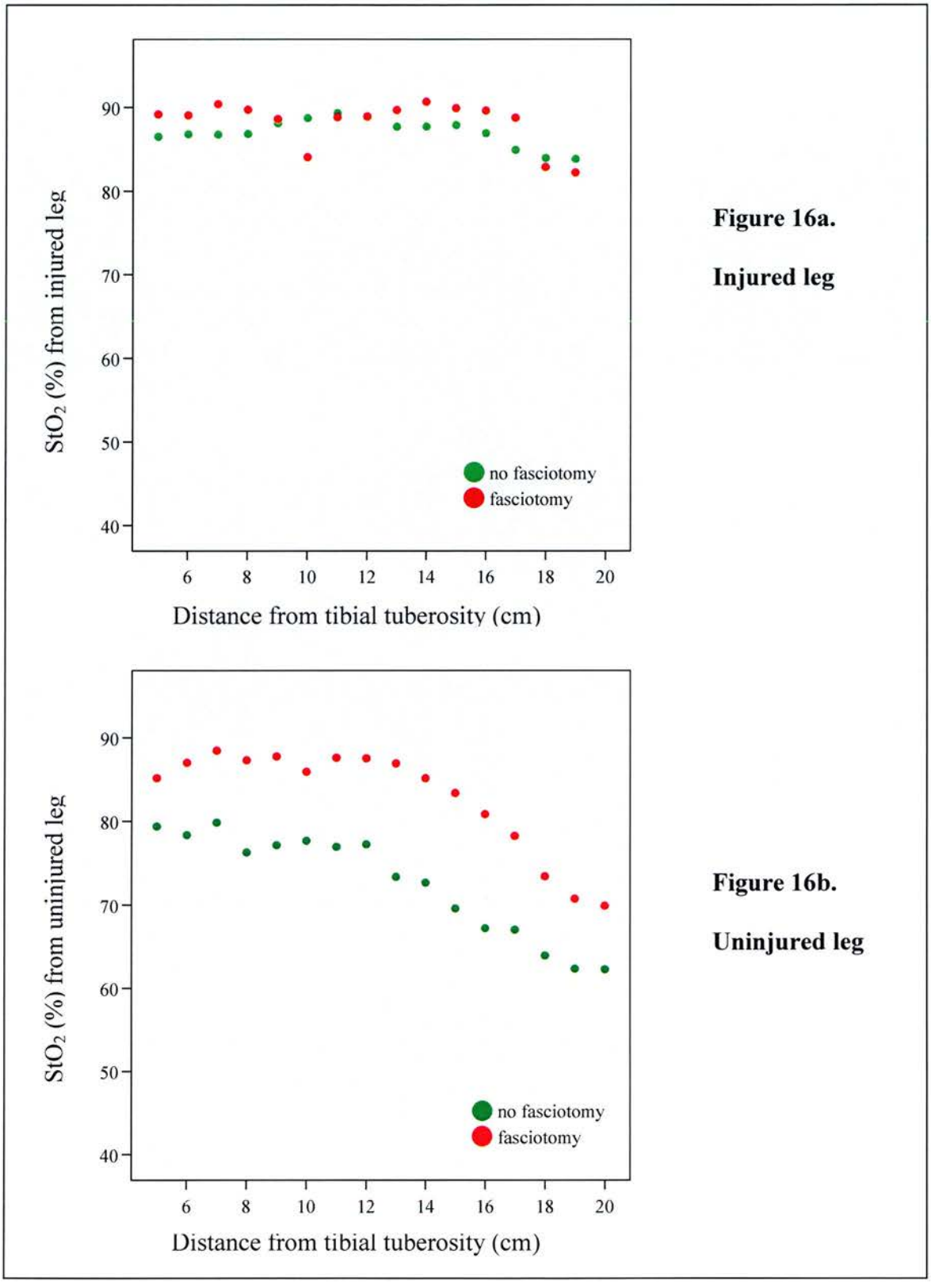

Figure 16a.

Injured leg

Figure 16b.

Uninjured leg

Figure 16 Mean StO_2 (%) measured over the anterior tibial compartment at 1cm intervals from the tibial tuberosity. Subjects divided by fasciotomy groups. Figure 15a and 15b represent mean values taken from injured and un-injured legs respectively. (n = 70 subjects)

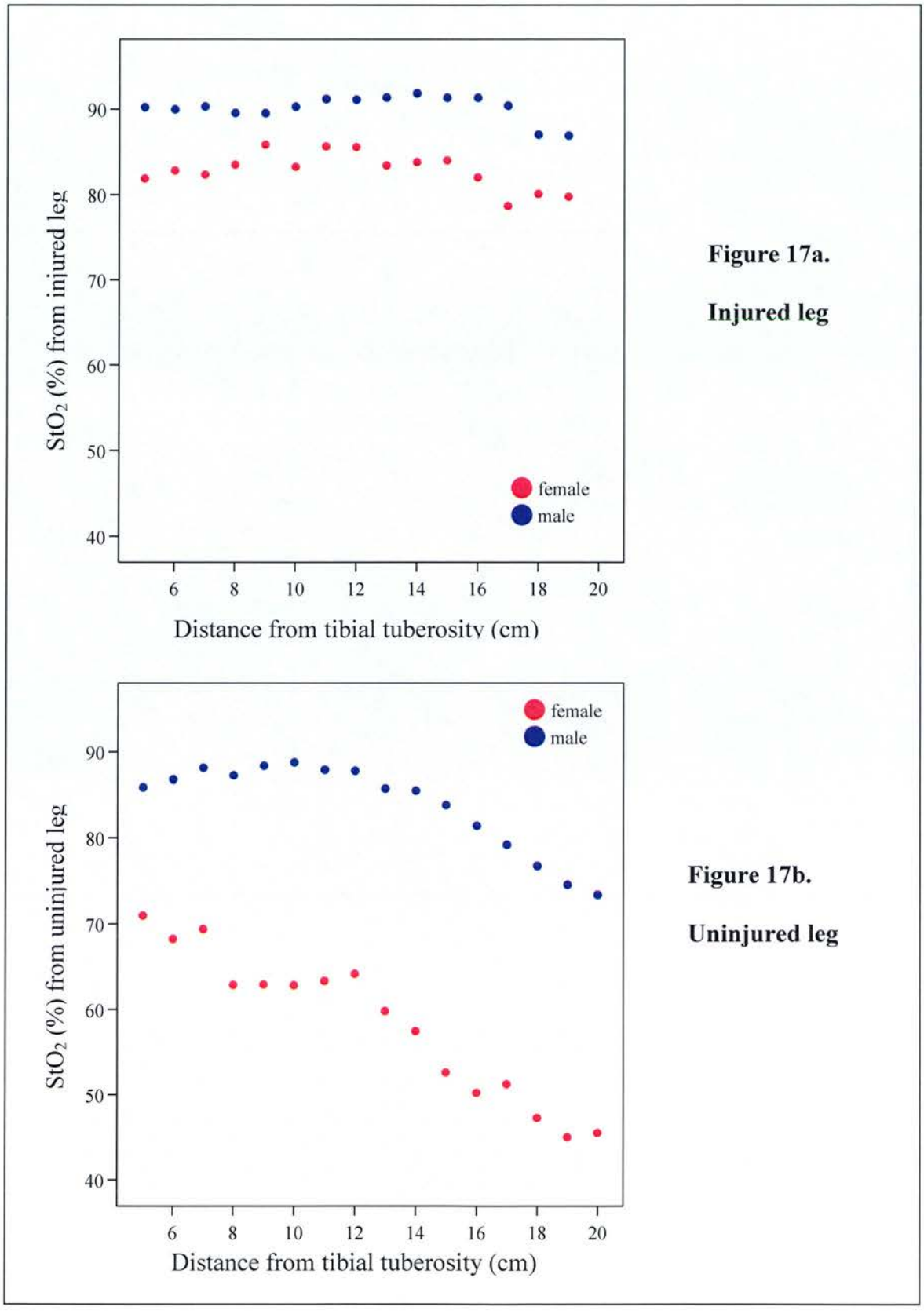

Figure 17a.

Injured leg

Figure 17b.

Uninjured leg

Figure 17 Mean StO_2 (%) measured over the anterior tibial compartment at 1cm intervals from the tibial tuberosity. Subjects divided by sex. Figure 16a and 16b represent mean values taken from injured and uninjured legs respectively. (n = 70 subjects)

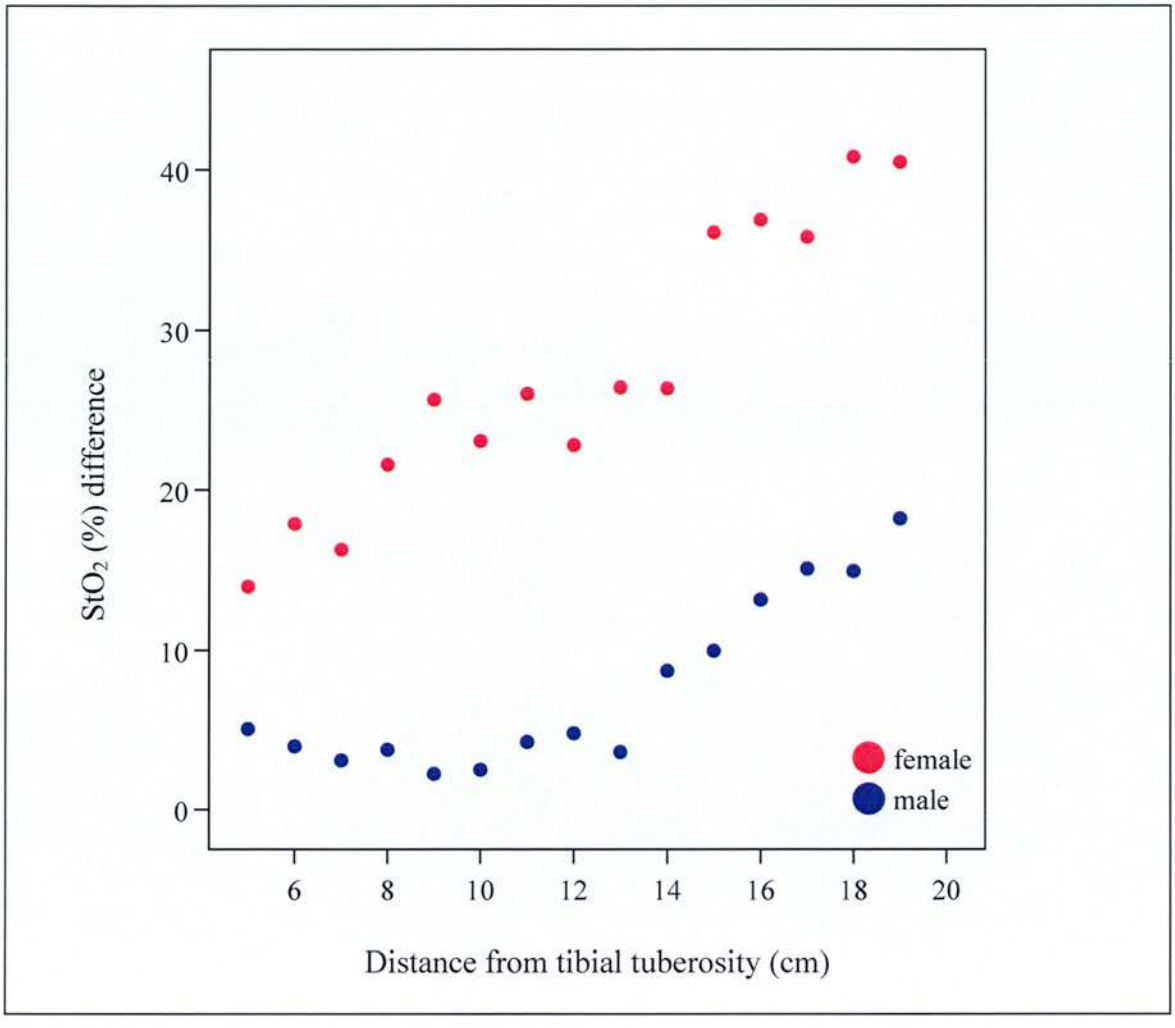

Figure 18 Mean StO_2 difference (%) measured over the anterior tibial compartment at 1cm intervals from the tibial tuberosity (n = 70 subjects). Mean differences between male and female = 20% ($p<0.01$)

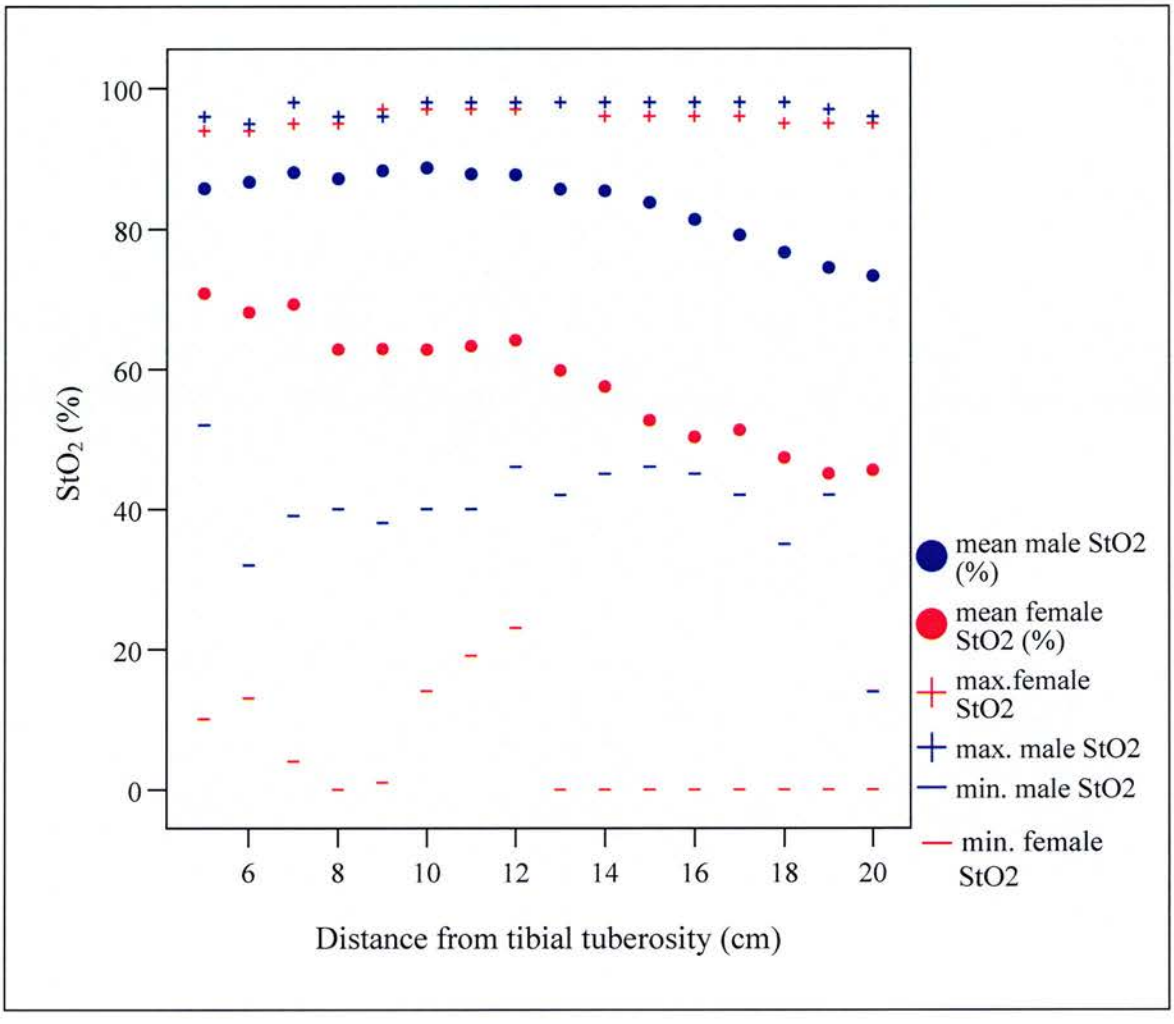

Figure 19 Mean StO_2 (%) measured over the anterior tibial compartment at 1cm intervals from the tibial tuberosity (n = 70 subjects). Mean values of StO_2 by sex and ranges are displayed.

In addition to measuring the StO_2 longitudinally over the anterior muscle compartment, a measurement of the StO_2 directly over the tibia was made 10 cm distal from the tibial tuberosity and 2 cm medial from the subcutaneous border of the tibia. This was carried out latterly during the study period and measurements were recorded on 18 tibial fractures and the corresponding uninjured leg at the same location. The values obtained over the bone were comparable to those over the muscle and again showed that the StO_2 was significantly raised in the injured leg compared to the uninjured side (Table 15).

Site of recording	**Mean StO_2 (%) (± SD) at 10cm from tibial tuberosity (n=18)**	**Mean difference (± SD)**	**Significance (paired samples t-test)**
Injured leg over muscle	89 (±5)	9(± 15)	p = 0.02**
Uninjured leg over muscle	79(± 17)		
Injured leg over bone	87(± 12)	16(± 19)	p < 0.01**
Uninjured leg over bone	71(± 21)		

Table 15 Comparison of StO_2 (%) between recordings over muscle and bone for 18 subjects. Mean difference = mean of differences between StO_2 for two sample groups

Ultrasound

Ultrasound measurements were carried out to identify if significant leg swelling took place during the monitoring period that could have influenced the non-invasive readings of StO_2. The ultrasound equipment became available for use from patient 41 onwards in the study. Measurements were taken of the distance, in centimetres, from the skin surface to the deep fascia 5 cm and 10 cm from the tibial tuberosity (Figure 20). These measurements were taken just prior to insertion of the invasive monitoring catheter and prior to a fasciotomy. If no fasciotomy was carried out, the measurements were repeated at the end of the invasive monitoring period. These measurements have demonstrated that during the pre-fasciotomy and invasive monitoring periods there was no significant increase in the skin to deep fascia distance in the fasciotomy patients that were measured. The only significant change in skin to fascia distance was in the 'no-fasciotomy' group 5 cm distally from the tibial tuberosity where a mean increase of 0.15 cm was detected (Table 16). In some cases the position of the catheter has not allowed for a repeat recording of the value at 5cms from the tibial tuberosity and therefore statistical calculation could not be carried out (Tables 16, 17). The results of a comparison of the skin to deep fascia distances between the injured and uninjured legs are shown in Table 17. There are significant differences in the skin to deep fascia distance at 10 cms from the tibial tuberosity for both fasciotomy and non-fasciotomy patients. These differences were present at the time of initial invasive monitoring and when monitoring was discontinued. The mean difference in skin to deep fascia distance prior to fasciotomy was 0.47 cm compared to 0.27 cm at the end of monitoring for non-fasciotomy patients. This greater increase for these fasciotomy patients is important with respect to interpreting the StO_2 data, but the difference was not significant ($p = 0.2$) with a sample size of only four fasciotomy patients.

A comparison of the skin to deep fascia distance over the muscle at 10 cm from the tibial tuberosity for male and female patients reveals that there is a significantly greater depth of tissue superficial to the fascia in female subjects on admission. This difference is found on both the injured and uninjured legs. On completion of the monitoring the increased depth found in female subjects had decreased to a non-significant level on the injured side. At the end of monitoring the soft tissue depth between the skin and fascia for the uninjured leg remained significantly greater for female subjects despite a slight decrease for both sexes (Table 18).

Ultrasound allowed measurements within the anterior compartment to be carried out. Values of the distance from the fascia to the posterior border of tibialis anterior muscle were measured (Figure 20).

The mean depth of tibialis anterior prior to fasciotomy for 6 cases was 1.15 cm compared to 1.11 cm for 26 non-fasciotomy cases ($p = 0.8$). In 20 males the mean depth was 1.21 cm relative to a mean depth of 0.98 cm in 12 females ($p = 0.02$). There was no significant difference in tibialis anterior depth in males between those who underwent fasciotomy and those who did not. The mean tibialis anterior depth was 1.15 cm and 1.23 cm respectively ($p=0.5$).

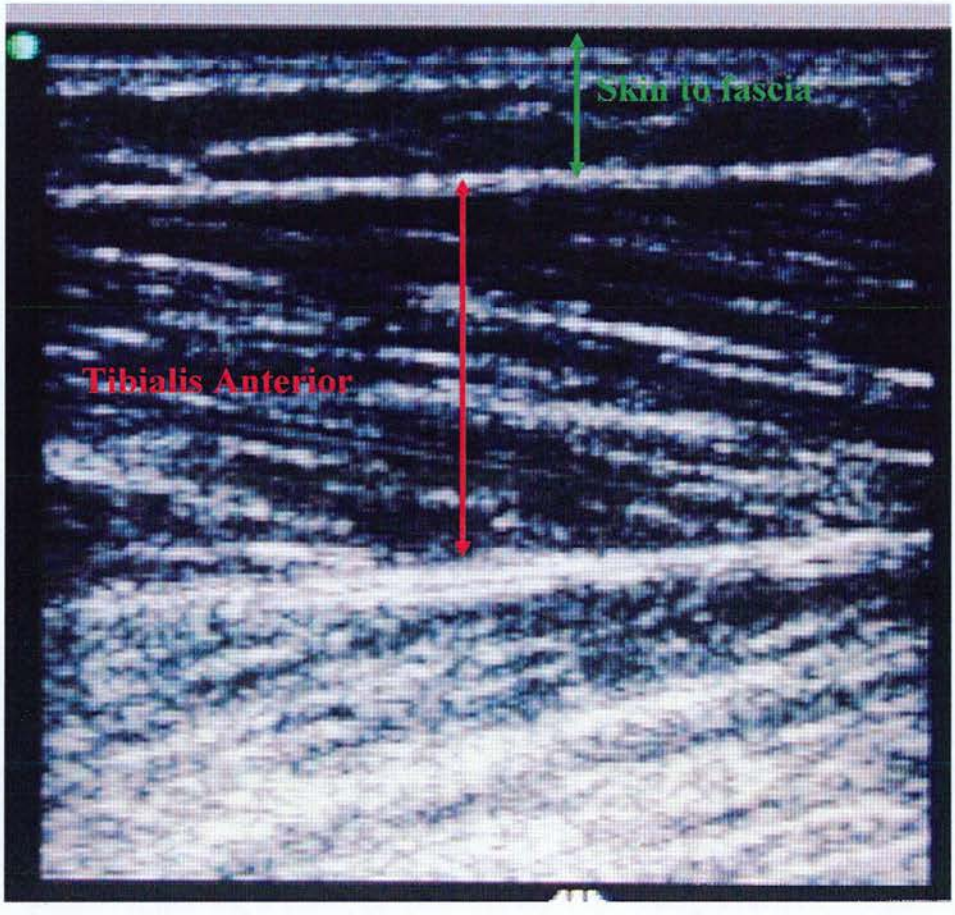

Figure 20 Ultrasound scan of superficial anterior leg compartment. Red arrow = distance from skin surface to deep fascia. Green arrow = deep fascia to posterior border of tibialis anterior

		Fasciotomy group	Admission mean skin to deep fascia distance(cm) (±SD)	significance	Pre-fasciotomy or end of monitoring mean skin to deep fascia distance (cm) (±SD)	significance	Mean difference (cm)	significance
Injured leg	5cms distal to tibial tuberosity	Fasciotomy (n=9)	0.56 (±0.26)	p = 0.5	0.47 (±0.07)	p = 0.4	-0.23	p = 0.7
		No fasciotomy (n=27)	0.64 (±0.37)		0.69 (±0.32)		0.15	p = 0.04
	10cms distal to tibial tuberosity	Fasciotomy (n=11)	0.79 (±0.56)	p = 0.7	0.71 (±0.32)	p = 0.9	0.05	p = 0.8
		No fasciotomy (n=37)	0.74 (±0.41)		0.74 (±0.36)		0.02	p = 0.7
Un-injured leg	5cms distal to tibial tuberosity	Fasciotomy (n=8)	0.45 (±0.13)	p= 0.3	0.43 (±0.05)	p = 0.6	a	
		No fasciotomy (n=30)	0.58 (±0.28)		0.53 (±0.28)		-0.05	p = 0.2
	10cms distal to tibial tuberosity	Fasciotomy (n=10)	0.48 (±0.21)	p = 0.4	0.37 (±0.08)	p = 0.3	0.01	p = 0.7
		No fasciotomy (n=35)	0.56 (±0.32)		0.50 (±0.24)		0.09	p = 0.1

a = not calculated as 'paired sample' data insufficient due to catheter position

Table 16 Mean distances between skin and deep fascia, measured by ultrasound (cm). Mean difference = mean of differences between admission values and values prior to fasciotomy or at the end of monitoring, significance calculated using paired samples t-test.

		Mean differences between injured and un-injured legs			
	Fasciotomy group	admission mean difference in distance skin to deep fascia (cm) (±SD)	significance	pre-fasciotomy or end of monitoring mean differnce in skin to deep fascia distance (cm) (±SD)	significance
5cms distal to tibial tuberosity	Fasciotomy (n=8)	0.04 (±0.11)	p = 0.3	a	
	No fasciotomy (n=26)	0.06 (±0.32)	p = 0.3	0.17 (±0.29)	p = 0.02
10cms distal to tibial tuberosity	Fasciotomy (n=10)	0.28 (±0.45)	p = 0.08	0.47 (±0.3)	p = 0.05
	No fasciotomy (n=35)	0.17 (±0.42)	p = 0.02	0.27 (±0.3)	p < 0.01

a = not calculated as 'paired sample' data insufficient due to catheter position

Table 17 Mean differences (cm) between injured and un-injured legs in distance between skin surface and deep fascia on admission and prior to fasciotomy or at end of monitoring period (for non-fasciotomy patients).

	sex	Admission mean skin to deep fascia distance(cm) (±SD)	significance	Pre-fasciotomy or end of monitoring mean skin to deep fascia distance (cm) (±SD)	significance
Injured leg	Male (n=32)	0.64 (±0.38)	p = 0.02	0.65 (±0.32)	p = 0.1
	Female (n=16)	0.98 (±0.48)		0.85 (±0.36)	
Un-injured leg	Male (n=31)	0.45 (±0.2)	p < 0.01	0.37 (±0.1)	p < 0.01
	Female (n=14)	0.76(±0.38)		0.67 (±0.28)	

Table 18 Mean distances between skin and deep fascia at 10 cms distal to tibial tuberosity for injured and un-injured legs on admission and at end of monitoring, grouped by gender.

Follow-up

Patients were followed up for regular clinical review in the outpatient department and were seen for follow up with regard to the study at approximately 6 months. Sixty-six patients (64%) were followed up at mean 5.6 months following injury (range 0.5 months to 12 months). Thirty-six patients were lost to follow up; this included 15 patients who were discharged early to other centres and 21 patients who did not attend or could not be seen by the author. Of the 66 patients seen, 62 were tibial fractures and 4 had sustained forearm fractures. The 62 tibial fracture patients included 56 treated by an intramedullary (IM) tibial nail, two using an external fixator, two by means of plating and two who had been conservatively managed. Fifteen patients with a tibial fracture had undergone a fasciotomy.

Thirty-two patients (48%) reported persistent pain requiring regular analgesia at a mean of 5.8 months following their injury and treatment, compared to the rest (n=34) who reported being pain-free at a mean of 5.4 months. From the 32 patients with pain, six had leg pain, five had persistent ankle pain and 21 experienced knee pain, of which 19 had had a tibial fracture treated by an intra-medullary nail.

Distal sensory deficit was specifically sought for by using light touch and found to be present in nine cases, eight of which were tibial fractures treated by IM nailing, the other was altered sensation in the distribution of the superficial branch of the radial nerve following a forearm plating. From the eight legs with altered sensation, five had altered sensation in the first web space and two had sensory changes to the dorsum of the foot. From the five that had altered first web space sensation, two had undergone fasciotomies. The compartment pressures and StO_2 values for these patients are shown in table 19. The mean compartment pressures for the fasciotomy patients are elevated, whereas the StO_2 difference values are high. This is in contrast to the three other patients who did not have

a fasciotomy but had altered sensation and are seen to have had a low mean StO_2 difference.

	Case No.	Compartment pressure (mmHg)	ΔP (mmHg)	StO_2 injured leg (%)	StO_2 uninjured leg (%)	StO_2 difference (%)
fasciotomy	74	46	35	90	73	17
	91	69	32	95	71	24
No fasciotomy	34	28	39	79	91	-12
	51	22	64	91	90	1
	76	34	55	88	83	5

Table 19 Mean compartment pressure and StO_2 values for the five patients found to have persistent distal sensory deficit at follow up.

The presence of contractures was seen in only three patients who were followed up. One patient had an ankle inversion contracture; he had had a mean compartment pressures of 15 mmHg (ΔP 69 mmHg and StO_2 difference 19 %). A second patient had a flexion contracture of the knee; he had had a fasciotomy following a mean compartment pressure of 58 mmHg (ΔP 11 mmHg and StO_2 difference 2.6%). The third patient had flexion contractures of the second and third toes following a fasciotomy that was carried out 25 hours after IM nailing of the tibia. In this case the mean ΔP was 31mmHg and mean compartment pressure was 33 mmHg. The mean value does not reflect the steadily decreasing ΔP that was below 25 mmHg over the last 5 hours. The StO_2 difference fell steadily from 31% at nine hours post-operatively to 17% immediately prior to the fasciotomy.

Power in all muscle groups of patients examined during follow-up was found to be 4 or above on the MRC scale. Two patients who had forearm fractures were found to have

weakness in all movements of the wrist. One had undergone forearm plating, the other had been treated by an external fixator. One patient had weakness of eversion of the ankle following IM nailing of the tibia; she had had a mean compartment pressure of 23 mmHg (ΔP 30 mmHg) and a mean StO_2 difference of – 4%. No fasciotomy had been carried out. A final patient had weakness of ankle inversion also following a tibial fracture and IM nailing and no fasciotomy. He had mean values of compartment pressure 16 mmHg, ΔP 69 mmHg and StO_2 difference 19%.

Follow up of the 66 patients revealed seven recognised complications, but in addition six patients required nails to be removed for pain and six patients had late removal of locking screws. Delayed union was identified in three patients, two of whom required exchange IM nailing. These three patients had not had a fasciotomy and their mean ΔP values were 47, 41 and 44mmHg. There were three wound infections that comprised one infected split skin graft, an infected proximal tibial wound and an infected pin site. All were managed with oral antibiotics. One patient, a male diabetic, required a below knee amputation due to massive muscle necrosis in the lower leg following the development of an acute compartment syndrome after IM nailing of a 3B open tibial shaft fracture. His nailing was carried out at five hours from admission and he required a fasciotomy four hours later. The rapid rise in compartment pressure is reflected in the fall in ΔP values. The StO_2 difference demonstrated a fall from 8% to 2% during the interval between IM nailing and fasciotomy (Figure 21). Spontaneous acute compartment syndrome in diabetic patients has been described and associated with massive muscle infarction and necrosis (Chautens *et al*, 1997; Smith and Laing, 1999)

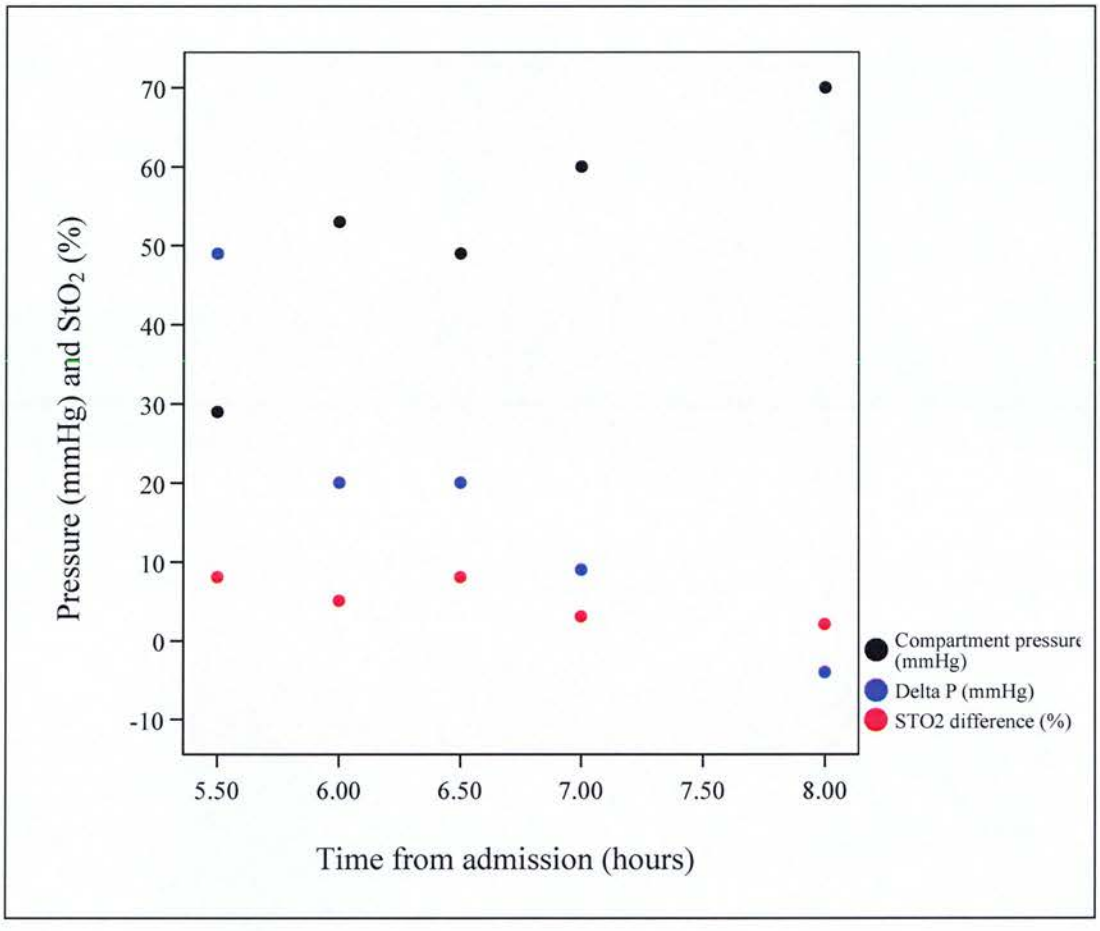

Figure 21 Case No 9. Values of compartment pressure (mmHg), ΔP (mmHg) and StO_2 difference (%). Time period reflects interval between IM nailing and fasciotomy.

Diagnostic effectiveness of non-invasive StO_2 measurements

For this study, the effectiveness of non-invasive StO_2 measurements as a predictor of acute compartment syndrome has been compared to that of ΔP using a threshold value of 30mmHg for decompression (McQueen and Court-Brown, 1996). Assuming that when a fasciotomy had been carried out, this indicated the presence of an acute compartment syndrome, then it was possible to compare the accuracy of StO_2 measurements with pressure measurements. As the decision to carry out a fasciotomy was dependant on ΔP values then any other diagnostic tool was unlikely to improve on the accuracy of pressure measurements. The follow-up of patients has allowed three patients to be identified who had clinical signs suggestive of a previous acute compartment syndrome that have not had a fasciotomy, *i.e.* false negatives. In this study it was not possible to identify accurately any patients who may not have had an acute compartment syndrome yet had a fasciotomy, *i.e.* false positives. Receiver operating curves have been plotted both excluding the false negatives and also including the false negatives (three patients – table 19). Curves have been drawn to show the sensitivity and specificity of compartment pressure, ΔP, StO_2 injured leg and StO_2 difference (Figure 22). These calculations have been carried out to examine the ability of any single reading being able to predict the endpoint of a fasciotomy (Figure 22a) or fasciotomy and possible false negative diagnoses (Figure 22b).

The receiver operator curves (ROC) indicate that using a single measurement of compartment pressure, ΔP, or StO_2 difference would be significantly better than guessing the outcome for any individual case ($p < 0.01$). A single measurement of the StO_2 on the injured leg, however, is no better than guessing the endpoint. The area beneath the curves reflects the degree of accuracy of the individual tests (Table 20). Measurements of compartment pressure and ΔP were at least 85% accurate compared to StO_2 difference of 68%.

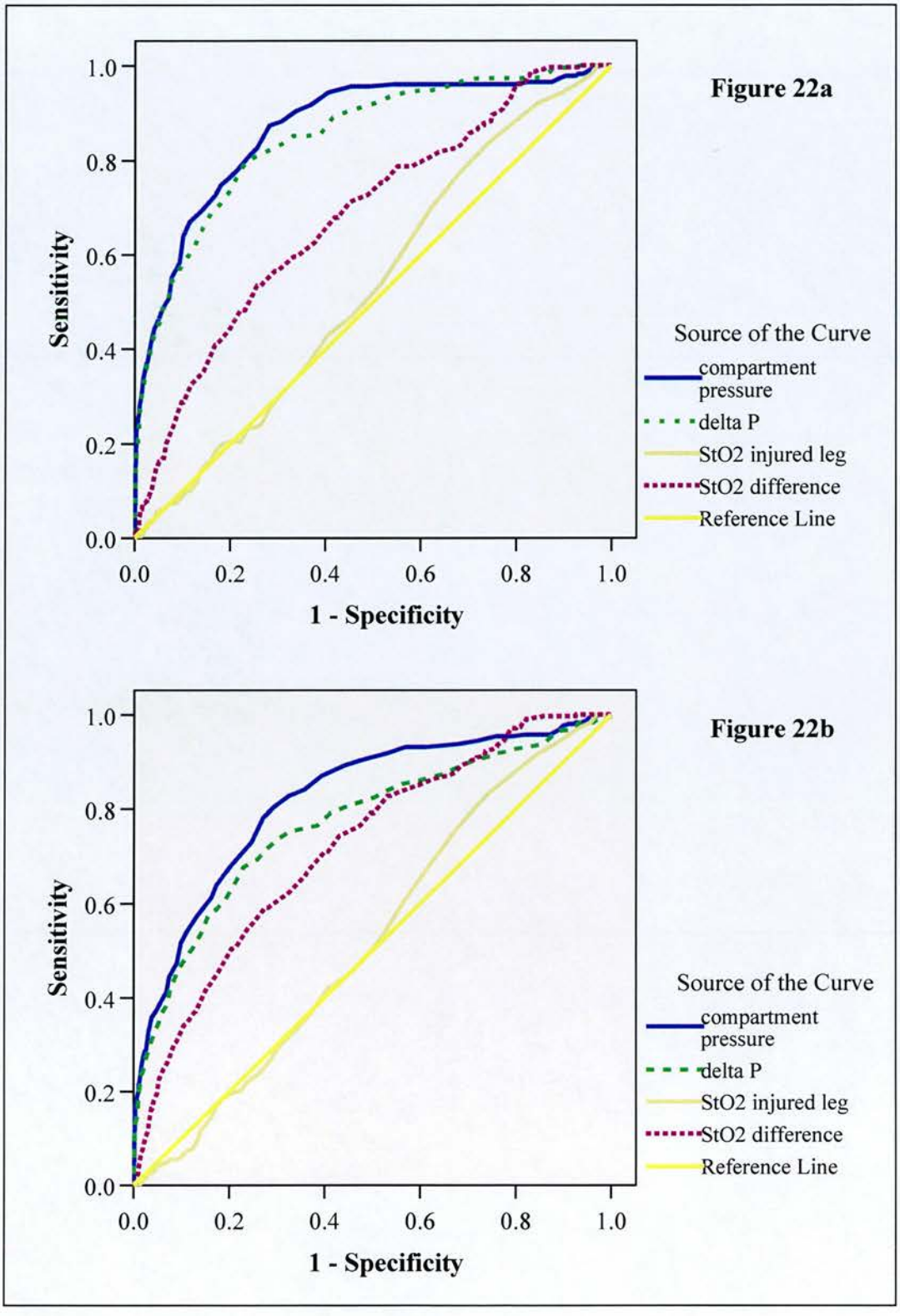

Figure 22 Receiver operator curves, indicating sensitivity and specificity of using compartment pressure, ΔP, StO_2 injured leg and StO_2 difference. Figure 22a is calculated using fasciotomy alone as the endpoint. Figure 22b uses the endpoint of an acute compartment syndrome (fasciotomy and presence of altered sensation at follow up).

Test	Accuracy	Significance	95% Confidence Limit	
			Lower limit	Upper limit
compartment pressure	86%	$p < 0.01$	84%	89%
ΔP	85%	$p < 0.01$	82%	87%
StO_2 injured leg	53%	$p = 0.1$	49%	57%
StO_2 difference	68%	$p < 0.01$	64%	72%

Table 20 Accuracy of compartment pressure, ΔP, StO_2 injured leg and StO_2 difference as tests to predict from a single value the outcome (when endpoint = fasciotomy). 95% confidence limits shown.

The three patients who had altered sensation in their first web space may have developed an acute compartment syndrome without diagnosis and not had a decompression. When these three patients are included as compartment syndrome cases then the ROC curves can be plotted as in Figure 22b. The accuracy of the compartment pressure, ΔP, StO_2 injured leg and StO_2 difference as tests would then be 82%, 77%, 52% and 72% respectively.

Physiological variations.

In order to explain the wide variation in StO_2 measurements amongst the subjects, relationships between basic physiological parameters have been analysed. The mean StO_2 measurements from the uninjured limbs have been compared to the height, weight, body mass index (BMI), age and mean arterial blood pressure of each patient (Figures 23 – 26). In this situation the uninjured limb is not an ideal control as blood flow to the uninjured limb, and hence StO_2 measurements, may be affected by the injury on the contralateral side, an observation referred to as the 'steal effect' on blood flow (Nutton *et al.*, 1984). However, for the purposes of identifying possible variables, all subjects have sustained an injury on the contralateral limb and therefore the resultant physiological responses have been assumed to be similar in all patients.

It has been found that the mean StO_2 measured from the uninjured limb was significantly correlated with the height of females. As the height of an individual increased the StO_2 increased. The mean StO_2 was significantly influenced by the weight of the subject in both female and male patients (Figure 25). With regard to the weight of an individual, male subjects showed a more constant StO_2, remaining predominantly above 80%. The female subjects however demonstrated a sharp fall in StO_2 as the weight of an individual increased. The ranges of StO_2 from the uninjured limb were more widely spread for women as compared to men.

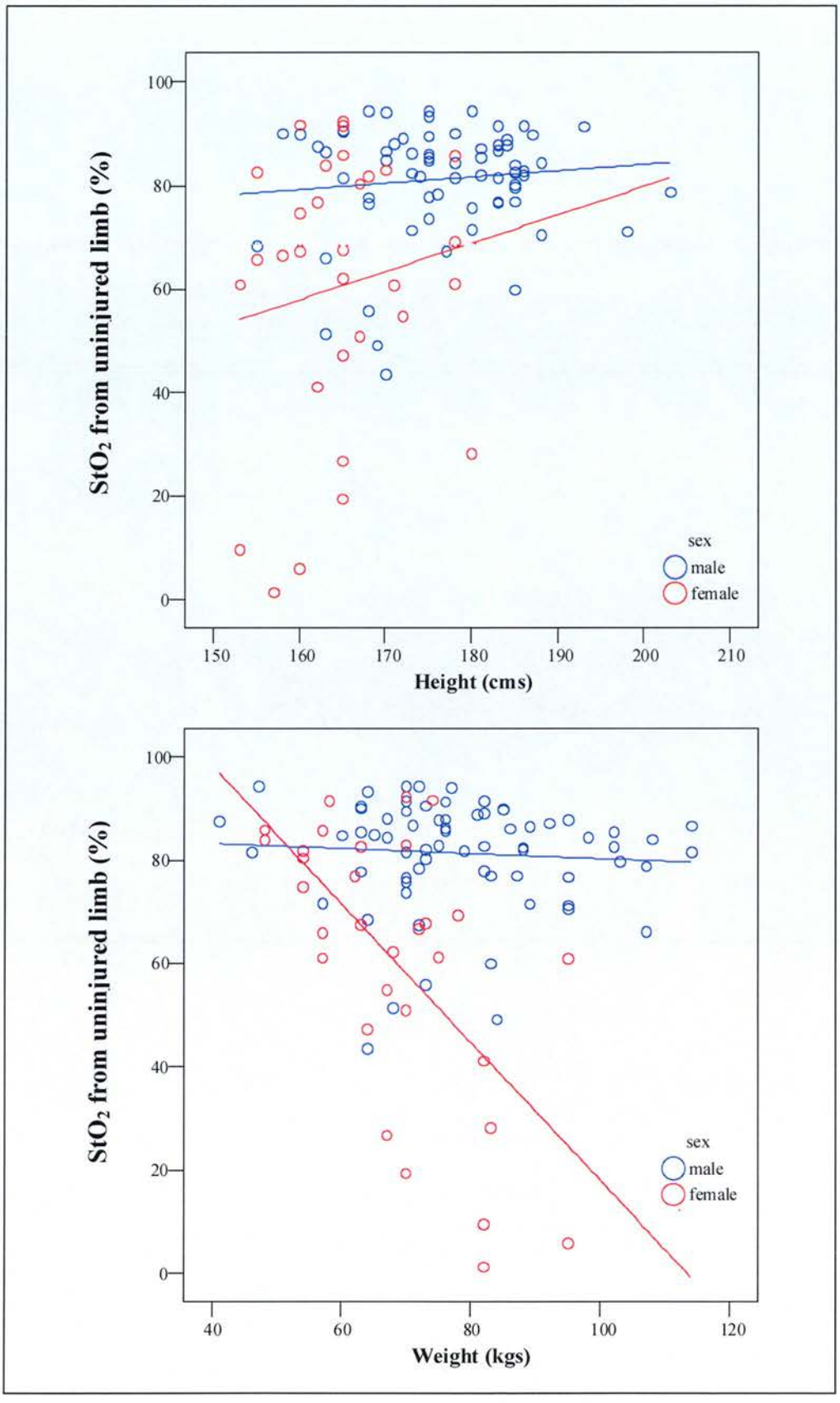

Figure 23 Height (cms) and weight (kgs) of clinical study subjects by mean StO_2 of uninjured limbs. Labelled by sex. Points represent single subjects. Correlation Spearman's rho (Height by StO_2) males = 0.02 ($p = 0.4$), females 0.10 ($p < 0.01$). Correlation Spearman's rho (Weight by StO_2) males - 0.05 ($p = 0.05$), females: $r = - 0.58$ ($p < 0.01$).

When the body mass index is calculated (weight.height^{-2}) the relationship to the StO_2 of the uninjured limb is similar to that with the weight alone (Figure 24). The relationship of subject age to StO_2 of the uninjured limb is also significant, but differs in that older men demonstrate a decrease in StO_2 whereas women demonstrate a rise in the uninjured limb StO_2 with increasing age.

The relationship of StO_2 of the uninjured limb to age may in part be associated with the variation in BMI with age. Males demonstrated increasing BMI with age whereas for females the converse was true (Figure 25 top). The analysis of height compared to weight for male and female subjects indicates that the weight of male subjects increased as they became taller, compared to female individuals where there was little increase in height with increased weight (Figure 25 bottom). This illustrates that underlying physiological differences between the sexes with regard to soft tissue composition or distribution may be responsible for the clear differences in StO_2 measurements of the uninjured limb in men and women.

Mean arterial blood pressure for all subjects varied between 70mmHg and 130mmHg (Figure 26). The relationship with StO_2 measurements of the uninjured limb was nearly horizontal for both sexes, indicating only a small influence of MABP on the StO_2 values. MABP was more closely correlated to BMI (correlation = 0.2, $p < 0.01$).

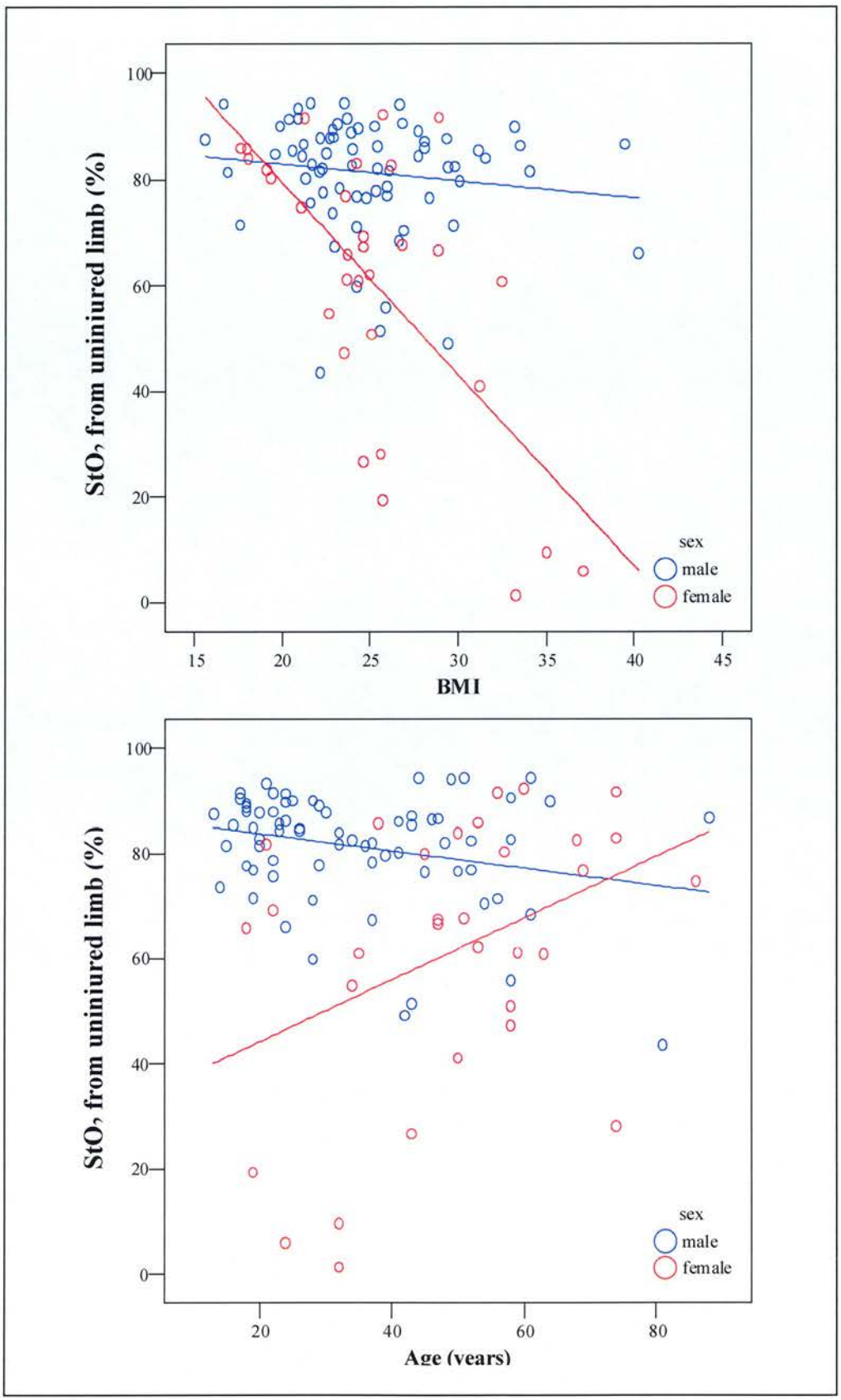

Figure 24 BMI and ages (years) of clinical study subjects by mean StO_2 of un-injured limbs. Labelled by sex. Points represent single subjects. Correlation Spearman's rho (BMI by StO_2) males = -0.10 ($p < 0.01$), females = -0.60 ($p < 0.01$). Correlation Spearman's rho (Age by StO_2) males = -0.1 ($p < 0.01$), females = 0.31 ($p < 0.01$).

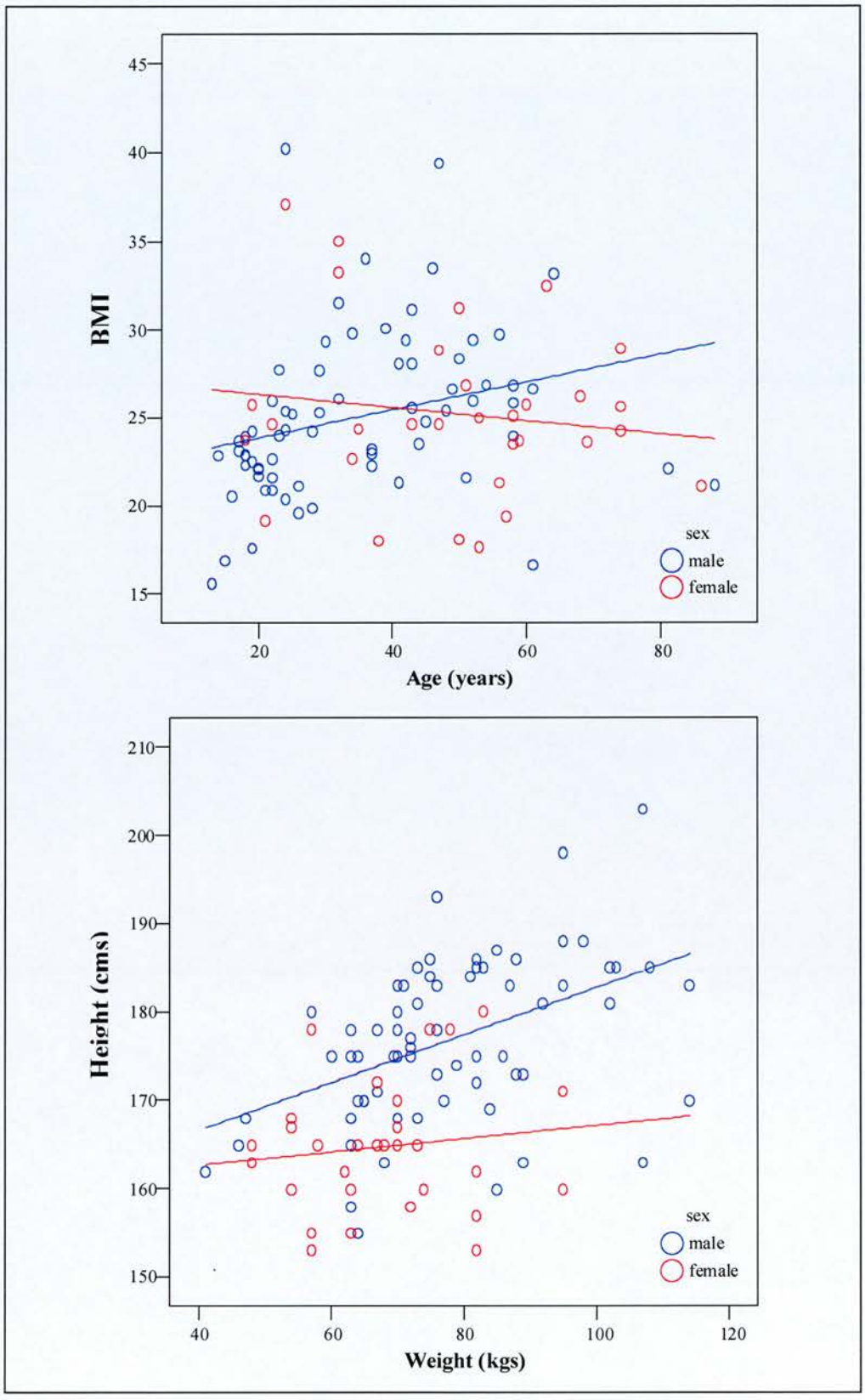

Figure 25 BMI by ages (years) of clinical study subjects (above) and height (cms) by weight (kgs) of clinical subjects (below). Labelled by sex. Points represent single subjects. Correlation Spearman's rho (BMI by age) males = 0.34 ($p < 0.01$), females = - 0.08 ($p < 0.05$). Correlation Spearman's rho (height by weight) males = 0.42 ($p < 0.01$), females = 0.20 ($p < 0.01$).

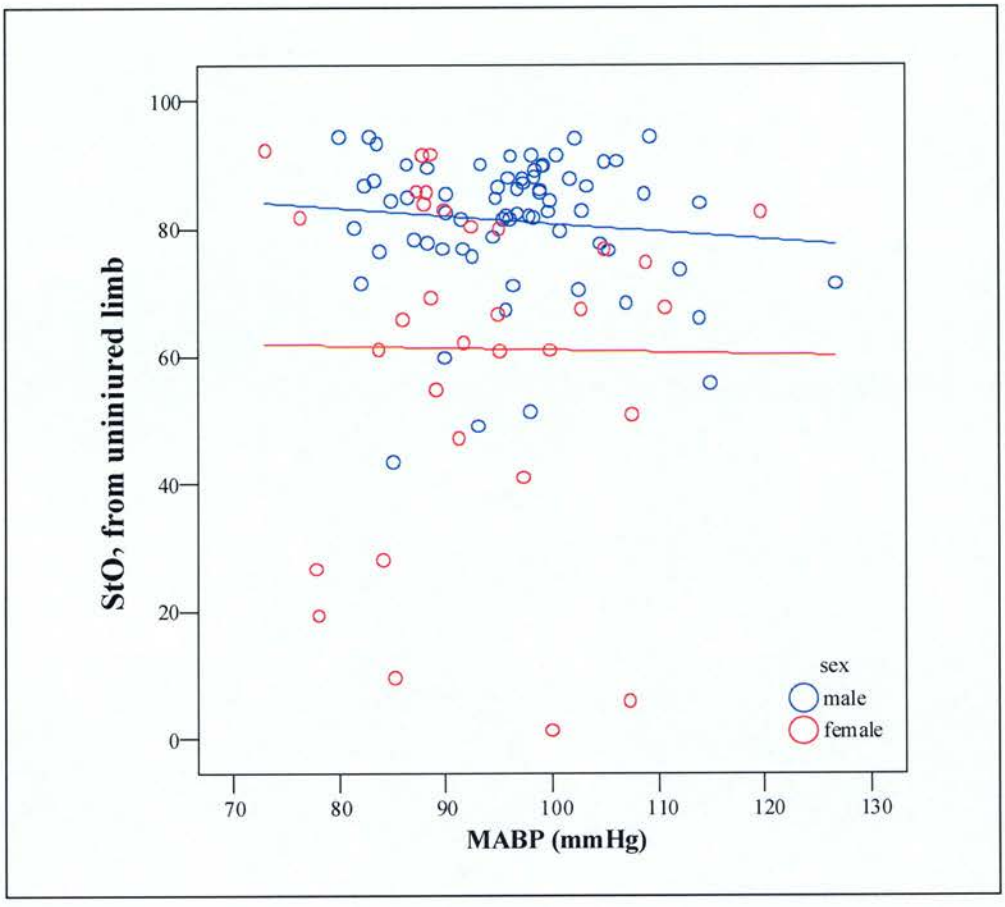

Figure 26 MABP (mmHg) of clinical study subjects and mean StO_2 uninjured limbs. Labelled by sex. Points represent single subjects. Correlation Spearman's rho males = - 0.1 (p = 0.7), female = - 0.01

Results of monitoring from an additional patient outside clinical study parameters.

During the course of the investigation a patient (42 years old) with a history of high alcohol intake and having had a previous transcutaneous intrahepatic porto-systemic shunt procedure was admitted with a four hour history of right lower leg pain, 18 hours after inversion injury to his right ankle without a fracture. He had altered distal sensation, muscle weakness and severe leg pain (Figure 27). He did not have pressure monitoring carried out and a clinical diagnosis of an acute compartment syndrome was made. With the consent of the patient, the NIRS monitor was applied over the anterior lower leg and StO_2 values were obtained (Table 21). There had been no localised trauma to the tissues over the anterior compartment and so the presence of any subcutaneous haematoma was unlikely. The fasciotomy revealed discoloured muscle (Figure 28). This was not debrided and had returned to normal colour by forty-eight hours. This case, although anecdotal in nature, demonstrates that NIRS has the ability to detect an acute compartment syndrome.

Figure 27 Photograph of the legs of a patient who clinically developed an acute compartment syndrome of the right leg following an inversion injury to the ankle (note bruising). His coagulation was normal. The leg was swollen. Note the absence of bruising over the anterior compartment. The StO_2 recorded was 0% over one area of the anterior compartment (table 21).

Distance distal from tibial tuberosity (cms)	StO_2 (%) Right	StO_2 (%) Left
5	91	92
6	76	90
7	15	89
8	0	88
9	1	89
10	4	88
11	17	90
12	33	92
13	36	90
14	50	87
15	78	87

Table 21 Results for patient (male age 42 yrs with clinical acute compartment syndrome and no fracture right leg). Measurements were made over the length of the anterior compartments prior to his fasciotomy.

Figure 28 Operative photograph from patient in figure 66. Photograph of the fasciotomy wound over the anterior-lateral right leg immediately following the opening of the fascia of the anterior compartment. Note the wide gaping of the wound and the discolouration to the muscle in the centre of the wound.

2.4 Discussion of the Clinical Study

The purpose of the clinical section of this study was to compare invasive continuous compartment pressure monitoring with non-invasive near-infrared spectroscopic monitoring in a prospective sample of patients at risk of an acute compartment syndrome admitted following isolated lower or upper limb injury.

The main findings of this study were as follows:

- a statistically significant correlation has been demonstrated between the compartment pressure and NIRS monitoring;
- StO_2 measurements from the injured leg alone do not predict the outcome with regard to fasciotomy;
- the StO_2 difference between the injured and uninjured limbs can predict the outcome with regard to fasciotomy;
- a wide variability in NIRS recordings has been found, both between limbs and between patients;
- males have significantly higher values of StO_2 than females;
- males have a shorter distance between the skin and fascia than females;
- NIRS measurements correlate with BMI and age;
- The measurement of StO_2 along the length of the legs has indicated that StO_2 values fall from proximal to distal and that this effect is eliminated following the injury to the limb.

The only published clinical study of NIRS and compartment pressure monitoring describes nine patients with acute compartment syndrome (Giannotti *et al.*, 2000). The study was published after the present study had begun. Giannotti recruited patients with a mixed mechanism of injury including vascular and penetrating injuries.

There were only two patients who had developed an acute compartment syndrome following a fracture. Their sample was made up of 74% men. No comments were made regarding any sex differences with StO_2 measurements. The controls were made up from 33 other surgical patients without injury and also nine individuals with lower limb injuries with no signs or pressure recordings suggestive of acute compartment syndrome. Recordings were made over the three most easily accessible compartments of the leg, as well as over the deltoid muscle. They avoided NIRS over obvious haematoma on the injured legs; the reason for this was not reported. Giannotti and his co-workers found that the mean StO_2 value (±SD) for the injured legs with an acute compartment syndrome was 56% (±27%). The value for the uninjured leg was 80% (±20%). In this clinical study the comparable findings for the fasciotomy patients were 80% (±14%) in the injured leg and 81% (±10) for the uninjured leg. They commented on the fact that their patients had 'dramatic and unequivocal manifestations of compartment syndrome'. This is in contrast to the present study where the diagnosis of compartment syndrome using compartmental pressure monitoring alone is known to precede the clinical diagnosis by a mean of 16 hours (McQueen, *et al.,* 1996). The patients of the present study would therefore be at an early stage of developing an acute compartment syndrome and changes in StO_2 may be reduced. Giannotti commented on the wide variation in NIRS readings. He found two patients in the compartment syndrome group that, despite having dramatic clinical signs, had StO_2 measurements greater than 80% which were indistinguishable from the control patients. He postulated that the high values may be due to an increased ability of ischaemic muscle to extract oxygen. The clinical study reported in this thesis has also found some patients with high compartment pressures that required fasciotomy to have high StO_2 values. It is proposed that rather than an oxygen shunting effect, the high StO_2 values may be due to tissue damage and haematoma in the subcutaneous layers that then

interferes with the NIRS signal. It was noticed during the study that legs that were very bruised provided an inconsistent signal. This signal did not easily reach a steady value and occasionally no signal was available at all. This was in contrast to the uninjured limb where a steady signal was obtained without difficulty. The investigation of the effect of the subcutaneous haematoma is a subject addressed in the animal study. Giannotti reports that some control patients had StO_2 values that were in the range of the compartment syndrome patients. This is a similar finding to that of the present clinical study where there was considerable overlap between the 'fasciotomy' and 'no fasciotomy' groups. Giannotti supposes that this was an effect due to 'patient factors' such as 'fat in the tissues' or hypoperfusion of the extremity. The present study has identified a significant difference between the sexes with regard to the distance from the skin to the fascia over the anterior aspect of the leg (table 18). It has also been identified that there are significant sex differences with regard to the StO_2 value in the uninjured legs. This subject has been investigated further in the volunteer study.

The finding that the StO_2 from the injured limb alone did not predict the patient outcome with regard to fasciotomy is dependant on a number of factors. The StO_2 on the injured side did not fall as greatly as predicted from the animal models (Garr *et al.*, 1999, Arbabi *et al.*, 1999). This study has demonstrated that the injured limb, in the absence of an acute compartment syndrome, has an increased StO_2 value throughout the length of the muscle compartment. In contrast, the animal models did not have an acute compartment syndrome precipitated by an injury, and therefore there is no element of hyperaemia in response to injury. The lack of injury in the model could contribute to lower StO_2 values during the development of an acute compartment syndrome in comparison to the injured limbs in the clinical study. The patients in the clinical study fell into categories of low compartment pressure, borderline pressure and pressure diagnostic of compartment

syndrome on admission. It was only the borderline patients that returned to the ward that underwent post-fixation monitoring. These patients had StO_2 values from the injured limb before the fasciotomy that could be compared to values taken on admission. This group comprised only 10 patients and the difference was not statistically significant either due to the low numbers or the variability of measurements. Patients in this study all had continuous compartment pressure monitoring, which allows early diagnosis of an acute compartment syndrome (McQueen, *et al.,* 1996), and therefore it is possible that more profound ischaemic changes may have been seen at lower values of ΔP. NIRS monitoring of muscle after a fasciotomy was not possible in this study as a sterile version of the patient interface for the InSpectra^{TM} was not available. The collection of pre-fasciotomy and post-fasciotomy values on the injured limb would have allowed a comparison for each of the fasciotomy patients so that ischaemic and non-ischaemic values could have been established.

It has not been possible to establish a useful normal range for the StO_2 using the InSpectra^{TM}. To carry out an investigation to examine StO_2 levels a control needs to be defined. Previous studies have used other patients or volunteers to define the normal range (Giannotti *et al.*, 2000; Gentillelo *et al.*, 2001) or even a site on the upper limb when investigating a lower limb (Giannotti *et al.*, 2000). The above options do not control for the intra-patient and inter-patient variability that has been found with NIRS in this study. The use of the uninjured contralateral limb has been chosen as the control in this study. It is not a 'normal' limb for that patient in view of the physiological effects of blood flow reduction known as the 'steal phenomenon' (Nutton *et al.,* 1984). In making comparisons between sides, ideally the only factor affecting StO_2 should be that produced by the injury itself. Having had an injury, there are additional differences such as that of dressings, which could affect limb and skin temperature, differences in bruising and differences in

swelling between injured and un-injured limbs. The influence of swelling was therefore examined in the clinical part of this study alongside the measurements for StO_2 and compartment pressure. Significant swelling was found at 10 cm from the tibial tuberosity in all patients with a leg injury irrespective of the fasciotomy requirement. The swelling was greater for those requiring a fasciotomy. This swelling could account for differences in StO_2 levels between the fasciotomy and the non-fasciotomy groups. An increase in distance between the skin and fascia, without an injury, is possibly related to a reduction in the StO_2 value. This could be the mechanism for reduced StO_2 measurements in fasciotomy patients. This effect of the skin to fascia distance on StO_2 measurements is investigated in the volunteer study of this thesis.

The comparison between the StO_2 and compartment pressure revealed a statistically significant correlation. When examined closely, this correlation held for males but not females. A similar correlation was found between the StO_2 difference and the differential pressure (ΔP). These correlations are statistically significant, but their gradients (coefficients) are shallow and therefore clinical interpretation would be difficult in view of the range of variability of the baseline readings of StO_2. Correlation of StO_2 and compartment pressures was not reported following the clinical study by Giannotti and co-authors (2000). A significant negative correlation ($r = 0.78$; $p < 0.001$) between levels of oxyhaemoglobin (measured by NIRS) and compartment pressure was reported from the acute compartment syndrome animal model (Garr et al., 1999). This correlation, as well as being significant, was felt to be clinically important and formed the basis of the progression towards a clinical trial of NIRS in patients at risk of an acute compartment syndrome.

The measurement of StO_2 along the length of the tibialis anterior muscle has not been previously reported. The observations made differed for the injured and un-injured

legs. For the un-injured legs, the values dropped significantly by a mean of 17% (±22%) from proximal to distal. The values started lower in female patients and again fell significantly towards the distal end of the leg. When the fasciotomy groups were examined, the non-fasciotomy group had significantly lower values than the fasciotomy group. This difference can be explained by the predominance of men in the fasciotomy group. The injured limb however, maintains the StO_2 along the length of the muscle. For females the effect of the injury on the values for StO_2 are most noticeable. This leads to a significantly greater StO_2 difference, of 20%, in women compared to men (Figure 18). To produce a diagnostic cut off for StO_2 difference then a separate value for the two sexes would be required. The rise in StO_2 as a result of the injury may be explained by a global rise in blood flow to the tissues. The increased blood flow response has been reported following re-perfusion after a prolonged period of ischaemia (Schaser *et al.*, 1999).

The potential limitations of this clinical study include the large number of excluded patients, a relatively high fasciotomy rate, incomplete monitoring data and a low follow-up rate.

In order to compare NIRS data to compartment pressure a large number of paired data points are required in both compartment syndrome and non-compartment syndrome cases. The purpose was to identify patients most at risk of a compartment syndrome so that ischaemic changes could hopefully be observed. There was only one NIRS device available for the clinical study and therefore if two patients were on the ward at the same time a decision was required to either continue monitoring with the first patient, or to change and enrol the second. If the second was in a higher risk group then the monitoring was discontinued and transferred to the new patient. On two occasions the monitoring was not transferred in order to enrol the next patient, these next patients then went on to require a fasciotomy.

The fasciotomy rate for the study was 21.6% and 15.3% for the excluded patients, giving a mean of 18.4%. A similar prospective study of 100 patients (104 fractures), but including children and polytrauma patients, reported a fasciotomy rate of 14.4% (Janzing and Broos, 2001). The study carried out in Edinburgh in the period 1988 to 1992 reported a fasciotomy rate of 4% for tibial fractures, 3.1% for forearm fractures and 0.25% for distal radial fractures. The reason for the increased rate of fasciotomy in the present study is unclear. Follow up allows the detection of patients with late sequelae of a missed acute compartment syndrome and therefore these cases can be added to the number of fasciotomies to calculate the rate of 'true compartment syndromes'. It is not possible, however to establish if any patients have had a fasciotomy that did not require one, *i.e.* false positives. [It is unlikely that a surgeon would report that their decision to carry out a fasciotomy was unnecessary.] Janzing (2001) calculated the sensitivity and specificity of a range of diagnostic criteria including clinical signs as well as compartment pressure measurements. Janzing applied the threshold for fasciotomy used in Edinburgh, of intra compartmental blood pressure subtracted from diastolic blood pressure being less than 30 mmHg, to his sample of patients and concluded that this would have given a fasciotomy rate of 45.4%. He points out that the study carried out by McQueen and Court-Brown (1996) used mean 12 hour values for their analysis. When this was applied to the Janzing data the fasciotomy rate was 9%. In reality, clinical decisions with regard to carrying out a fasciotomy are not made on single reading of ΔP, particularly in the presence of continuous compartmental monitoring. Some variation of the pressure readings can take place, for example with movement of the patient or transducer. Decisions to carry out a fasciotomy are therefore made on the changing trends in the data that is seen during the treatment of the patient. It is possible that the presence of a study and an additional monitoring device at the bedside heightens the awareness of the clinician in charge and

staff at the ward level to the diagnostic criteria of $\Delta P < 30$ mmHg suggested for fasciotomy. This could lead to a fasciotomy rate greater than those reported elsewhere. Janzing (2001) warns of the potential for 'over treatment' if diagnostic criteria are followed too rigidly.

This study had ten patients with incomplete recordings. This missing data affects the amount of paired data available for analysis between StO_2 and compartment pressures, but does not influence any correlation between individual values. The data from these patients therefore, was included in examining the correlation between StO_2 and compartment pressure. Patients without a full period of recording reduce the ability of the study to identify a predictive value of the StO_2 for diagnosing an acute compartment syndrome. Three patients had incomplete data due to the NIRS monitor not being able to detect a signal from the required site over the anterior leg compartment. In these cases it was possible to detect a signal elsewhere in the leg, in a similar fashion to the study carried by Giannotti (2000) where all compartments had been monitored. In his study the value corresponding to the highest compartment pressure was used for analysis. In the present study, the data was recorded as 'no signal' rather than moving the interface to a new site as it was known that the StO_2 varies with position on the limb. In validating an instrument for possible diagnostic purposes, it is important to record situations when the instrument does not perform as expected. Figure 26 shows the lateral fasciotomy wound of patient 55. In this case 'no signal' was available from the injured side over the anterior compartment both during the pre-fixation period and following IM nailing. The mean compartment pressure was 44 mmHg and ΔP 24 mmHg. The surface appearance of the leg at the fasciotomy, did not suggest any haematoma within the skin (Figure 29). It remains possible that the 'no signal' reading was due to interference by haematoma within the adipose tissue.

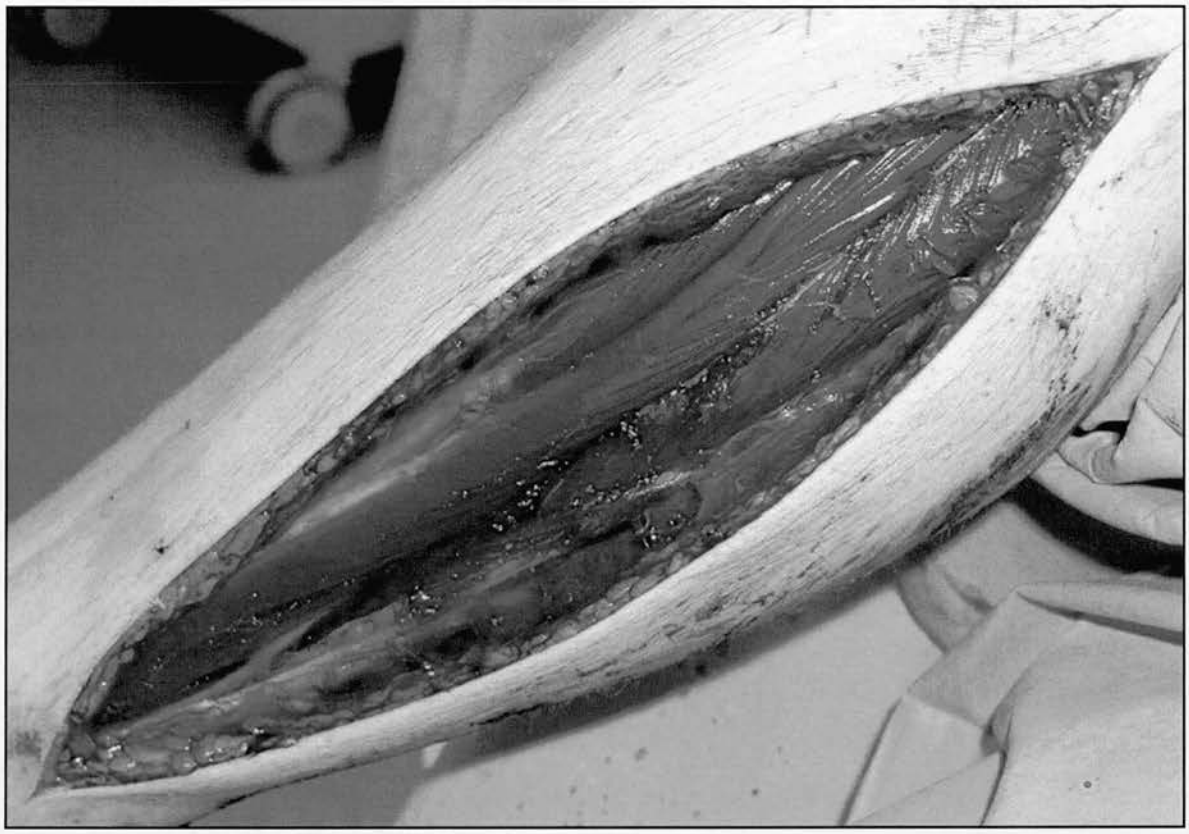

Figure 29 Lateral fasciotomy wound from patient 55 displaying anterior and lateral compartments and superficial peroneal nerve. No signal was detected over the anterior compartment. There was slight discolouration to the skin distally, but no distinct haematoma within the skin was seen. The muscles appeared viable at this fasciotomy.

This clinical study has a low follow up rate of 65%. The purpose of the follow up has been to establish the presence of late signs of acute compartment syndrome in patients who did not have a fasciotomy. Altered sensation on the first web space was detected in three patients. If these cases are added to the number of fasciotomies then a total of 25 cases of 'true acute compartment syndrome' can be assumed. This would give an acute compartment syndrome rate of 32%. As the follow up has only included approximately two thirds of the study patients then the rate of 'true fasciotomies' could be

higher. The design of the follow up had limitations due to the lack of the use of an established pain scoring system or validated examination of sensation.

This study has analysed patients according to their surgical management. Previous studies have either analysed single readings (Blick *et al.,* 1986) or in the case of continuous monitoring data has been analysed either as mean values over the whole period (Giannotti *et al.*, 2000) or divided into 12 hour means (McQueen and Court-Brown, 1996). Surgical management and the reduction of fractures is known to alter the compartment pressures (Shakespeare and Henderson, 1982) and therefore the time periods for part of the analysis were divided into periods according to the conservative or surgical management. This method allowed differences between the pre-fixation and post -fixation values to be identified. Patients with a pre-fixation compartment pressure of approximately 20 mmHg did not require a fasciotomy following IM nailing, whereas patients with a pre-fixation compartment pressure of approximately 35 mmHg ultimately required a fasciotomy after a period of ward monitoring. Those with pressures above 50 mmHg underwent immediate fasciotomy. Review of the admission times show that the delay from admission to first having a recorded pressure was between 5.2 hours and 6.4 hours for the four clinical pathway groups. This indicates that the difference in initial pressures between the clinical pathway groups is a feature of the injury or patient rather than a product of the time interval from the injury to the beginning of the compartment monitoring.

It has been recommended that the ideal position of the catheter for compartment pressure monitoring should be as close to the fracture as possible, as further from the fracture, the pressure within the compartment falls (Heckman *et al.*, 1994). This confirms that the compartment contents do not behave entirely as a fluid. In this study, monitoring using NIRS has taken place at one site over the anterior compartment. This was chosen in

the light of preliminary work with 12 volunteer legs in the Royal Infirmary of Edinburgh (unpublished data) that suggested the possibility of variability of StO_2 measurement with position. The position chosen of 10 cm distal to the tibial tuberosity provided the least variation. Observation during fasciotomies has identified clearly (Figure 15) a localised area of discolouration within the muscles that recover soon after the compartment has been decompressed. This observation may have been made possible by the relatively early decompressions in this study due to the criteria of decompression on compartment pressure alone and not waiting for clinical signs to develop. If there are 'watershed' areas, either physiological or anatomical, within the muscles with regard to the blood supply, then it is possible that the site chosen for NIRS monitoring in this study is an area that has well preserved perfusion. This would favour higher StO_2 measurements in the presence of increasing compartment pressure. The areas of striated discolouration, as in figure 14, were seen in the proximal portion of the lateral compartment rather than in the mid-point of the anterior compartment. If devices, either non-invasive or invasive, measuring StO_2 or other metabolites are to be useful diagnostically in early detection of acute compartment syndrome then a greater understanding of the local blow flow within the compartments is required.

2.5 Conclusion of the Clinical Study

This prospective clinical study, comparing near-infrared spectroscopic and compartment pressure monitoring, has shown a correlation between the StO_2 and the ΔP. Analysis of the results has identified possible sources of error due to patient and near-infrared spectroscopic variables and the discussion reveals some limitations of the study design. The remainder of this thesis examines more closely the effect of two possible variables that may have influenced this clinical study.

3 ANIMAL STUDY

3.1 Introduction

An animal model of acute compartment syndrome has been reported for the investigation of near-infrared spectroscopy as a technique for compartment monitoring. The animal used for the model was the pig (Garr *et al.*, 1999; Arbabi *et al.* 1999). This model has shown that compartment pressure in the anterior tibial compartment correlated inversely with soft tissue oxygenation, StO_2 (Garr *et al.*,1999). The lowest StO_2 was detected at the onset of the compartment syndrome. The induction of the compartment syndrome was indicated by loss of the ability to dorsiflex the foot on electrical stimulation of the common fibula nerve. Continued work with the porcine model revealed that near-infrared spectroscopy can detect an acute compartment syndrome in the presence of systemic hypoxaemia and hypotension. In this study the StO_2 over the anterior tibial compartment was reduced in the presence of hypoxaemia and hypotension, but with the addition of the compartment syndrome there was a further significant fall in the StO_2 of the involved compartment (Arbabi *et al.*,1999).

These animal models investigating NIRS have only used a compartment syndrome model where the soft tissues are normal. In the clinical situation limbs subjected to trauma will often have associated soft tissue injuries in conjunction with fractures. The clinical study in this thesis has indicated that there may be additional influences on the ability of NIRS to accurately detect an acute compartment syndrome. The animal model in this thesis investigated the hypothesis that near-infrared spectroscopic measurements are related to intra-compartmental pressure changes in a developing compartment syndrome in the leg with and without a subcutaneous or intramuscular haematoma.

3.2 Materials and Methods

Ethical approval for the animal study was sought and obtained from the Moredun Research Institute (Clinical Division), Penicuik, Scotland and the University of Edinburgh, Faculty Group of Medicine and Veterinary Medicine, Medical School, Edinburgh. Home Office approval was obtained under the ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986 - Scientific Procedures on Living Animals. Prior to Home Office approval, amendments were carried out to the Project Licence, held by the Harrison Law Professor of Orthopaedics, University of Edinburgh. Extensions to the experimental establishment and additions were required to the experimental techniques listed. A Personal Licence was successfully applied for by the author (Appendices G and H).

Animal Selection

In this study, as in previous studies of NIRS and compartment syndrome (Garr *et al.*, 1999; Arbabi *et al.,* 1999), the pig was chosen as the appropriate animal for the model. The reason for this is that the StO_2 is measured over 25 mm in depth from the skin surface. This depth is determined by the distance between the entry and exit of the near-infrared light on the skin surface (inter-optode separation) and is a feature of the instrument (InSpectra^{TM}) to be investigated. In addition it was possible to use the same design of instrument that was used in the clinical study, which would allow comparison of animal results with the clinical study. Post-mortem dissection of Landrace pig rear legs (pig mass: 70 kg and 250 kg) was carried out prior to the study beginning. Assuming a steady rate of growth, this indicated that a pig of mass 100-150 kg would have sufficient muscle mass in the anterior rear leg compartment for StO_2 measurements using near-infrared spectroscopy (Figure 30).

Fifteen semi-mature white Landrace pigs were provided by the Moredun Research Institute (Clinical Division), International Research Centre, Pentlands Science Park, Bush Loan, Penicuik, Scotland. The mean mass of the pigs was 104 kg (range 82 – 138 kg). Only one experimental animal was used per day.

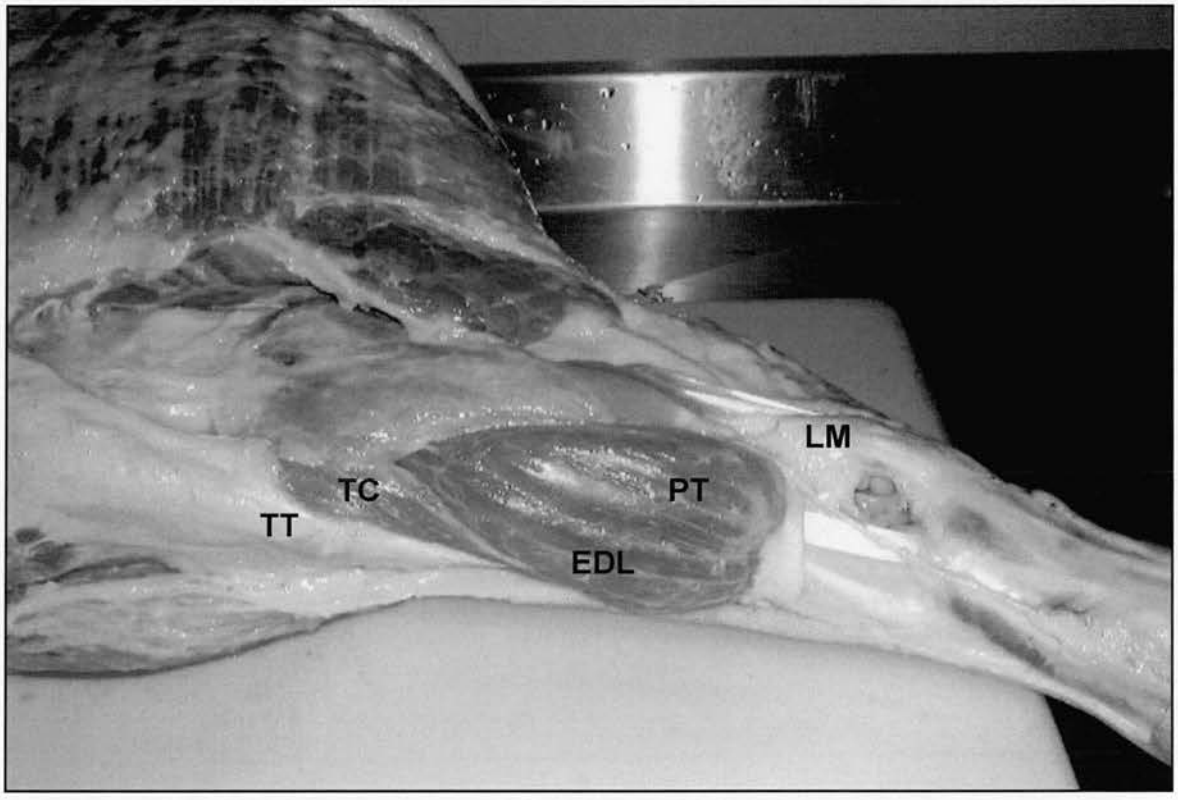

Figure 30 Dissection of Landrace pig (250kgs) left rear leg to show anterior compartment muscles, *Peroneus Tertius* (PT), *Extensor Digitorum Longus* (EDL) and *Tibialis Cranialis* (TC). Tibial Tuberosity (TT) and *Lateral Malleolus* (LM) are shown for orientation (Sisson *et al.*, 1975). Depth from skin to deep surface of anterior compartment muscles = 5 cm (1.5 cm skin and subcutaneous fat, 3.5 cm muscle).

Study Design

Preliminary statistical analysis was carried out by multilevel modelling of the data from previous animal work (obtained by permission, Garr *et al.*,1999). The analysis revealed that the minimum number of animals required (per group) to demonstrate the presence of a statistically significant correlation was five. An interim statistical analysis was therefore proposed following the first five animals in each group. If an important difference was found that did not reach statistical significance then the use of additional animals, up to ten in each group had been planned. The purpose of this was to minimize the number of experimental animals used.

Fifteen female *Landrace* pigs, mean mass 104.9 kg (SD ± 20.6), were divided into three groups of five animals each.

Group 1) **Intra-muscular plasma infusion -** Intra-muscular infusion of plasma only into anterior leg compartment.

Group 2) **Sub-cutaneous haematoma** - Subcutaneous injection of blood followed by intramuscular infusion of plasma into anterior leg compartment..

Group 3) **Intra-muscular haematoma** – Intra-muscular infusion of whole blood into anterior leg compartment.

Experiments were carried out in the following order group 3, then group 1 and then group 2. This allowed infusion with whole blood to be carried out on the first animal, as the production of plasma required the blood to stand for 24 hours. By rotation of experiments from one group to the next, this reduced the effect that any learning curve may have produced, that could have influenced the results if all the animals from one group alone had been completed before the next group had been started.

Anaesthesia

These experiments were carried out under terminal anaesthesia. All experimental procedures were carried out during the period of general anaesthesia.

During the immediate pre-operative period the pigs were deprived of food (and edible bedding) for 24 hours, but had access to water until pre-medication.

Pre-medication (Azaporone) was given prior to 'masking-down' using halothane. The animals were intubated and general anaesthesia was maintained using nitrous oxide and halothane.

In order to obtain a recording of the central arterial pressure, continuous arterial pressure monitoring via the right common carotid artery was carried out by insertion of an arterial catheter (20-guage Quick-Cath® II, Baxter) directly into the carotid artery following an open approach (technique observed at Rowett Research Institute, Aberdeen, 2001). The arterial catheter was tied in place and the carotid artery distal to the catheter was tied off. Oxygen saturation of peripheral tissues was monitored by pulse oximetry placed on the ear. A catheter was inserted into a peripheral vein on the ear of the pig for crystalloid infusion. Core temperature was monitored and recorded via a rectal transducer. Arterial blood gas sampling was carried out just prior to the start of any infusion (at time 0 min) and at the point of loss of anterior compartment muscle twitch.

Compartment Monitoring

For the duration of each procedure, continuous invasive pressure monitoring of the anterior tibial compartment was undertaken in the leg where the compartment syndrome was induced. This was carried out on the right hind limb. Non-invasive StO_2 monitoring took place on the same side using the interface of the InSpectra^{TM} Tissue Spectrometer. The recordings were made at intervals of five minutes. On the unaffected side (left) the

set up of catheters and non-invasive interface was identical to that on the right. For the unaffected side, recording of invasive and non-invasive data took place at the same intervals of five minutes. Before application and insertion of monitors, the skin over the anterior compartments was shaved. This was for ease of application of the adhesive patch that accompanies the spectrometer interface. The removal of hair was not expected to influence any data collected (Pringle *et al.*, 1999). Invasive compartment pressure monitoring was carried out using a slit catheter connected via a saline filled line to a transducer and monitor (Rorabeck *et al.*, 1981). This was the standard procedure for compartment pressure monitoring carried out in the Edinburgh Orthopaedic Trauma Unit and was used for the clinical study of this thesis. The catheter tip was positioned to record pressure from the central portion of the anterior tibial compartment. This corresponded with the portion of muscle over which the near-infrared spectrometer interface was situated. The position of the catheter tip was confirmed using a portable ultrasound scanner. The differential pressure (ΔP) was calculated as the diastolic blood pressure minus the compartment pressure (Whitesides *et al.,* 1975; McQueen, 1996).

In order to provide data to validate the measurements of the near-infrared spectrometer, a tissue monitor (Paratrend^{TM}, Biomedical Sensors, High Wycombe, UK) that recorded pH, temperature, partial pressure of oxygen (pO_2) and carbon dioxide (pCO_2) was used in addition to the invasive pressure catheter and the non-invasive near-infrared spectrometer (Hoffman *et al.,* 1996). This was inserted into the anterior compartments of the compartment syndrome leg following the induction of anaesthesia until thirty minutes after the fasciotomy took place at which time the procedure was finished. At the end of each procedure the invasive pH, pCO_2 and pO_2 catheter was placed into the infusion syringes and allowed to stabilise. This was to establish the gas make-up of the plasma and whole blood being infused to ensure that the measurements made in the

muscle compartments of the leg were not merely a reflection of the gas concentrations of the infusions and that any changes detected were a result of local tissue effects.

Compartment pressures, NIRS recordings and invasive pH, pCO_2 and pO_2 values were monitored continuously during the procedure and the times of changes in conditions, plasma infusion and fasciotomy were recorded alongside the data collected. Figure 31 demonstrates the set up of the catheters on a right, compartment syndrome leg.

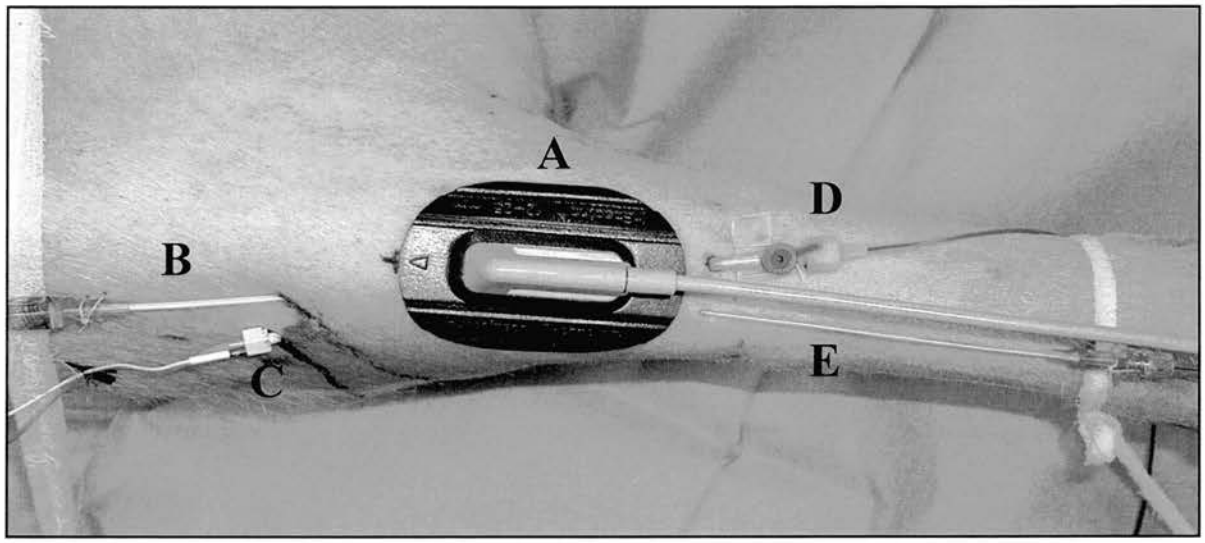

Figure 31 Experimental set-up of catheters on the acute compartment syndrome (right) leg.

A – near-infrared spectrometer interface

B – slit catheter compartment pressure monitor

C – nerve stimulator on the peroneal nerve

D – infusion catheter (plasma or whole blood)

E – invasive pO_2, pCO_2 and pH monitor

Induction of Acute Compartment Syndrome

The intra-compartmental infusions of plasma or whole blood were carried out via 18-gauge catheters inserted through the fascia to the mid-point of the anterior compartment muscles, beneath the non-invasive monitor. The infusions were created by the use of an infusion driver (Graseby Medical Ltd., Harts, UK) set to infuse a known volume per minute. The infusion pump was found to produce a pressure of mean 247 (range 211 – 270) mmHg before indicating 'tube occluded'. A single length of infusion tube was used. The length of tube was not found to affect the pressure at which the infusion driver indicated 'tube occluded' (preliminary experimental work, Royal Infirmary of Edinburgh, 2001). An initial experiment was set up using a 100 ml bag of saline, to represent the anterior compartment, which was connected to the infusion pump and pressure transducer. The bag was filled at both 10 ml per hour and at 20 ml per hour and the pressure recorded (Figure 32 - preliminary work, Royal Infirmary of Edinburgh, 2001). It was predicted that a volume of 50-100 ml blood or plasma would be required per animal. The initial rate of infusion was set at 20 ml per hour such that the compartment syndrome would be induced within a period of 2-4 hours.

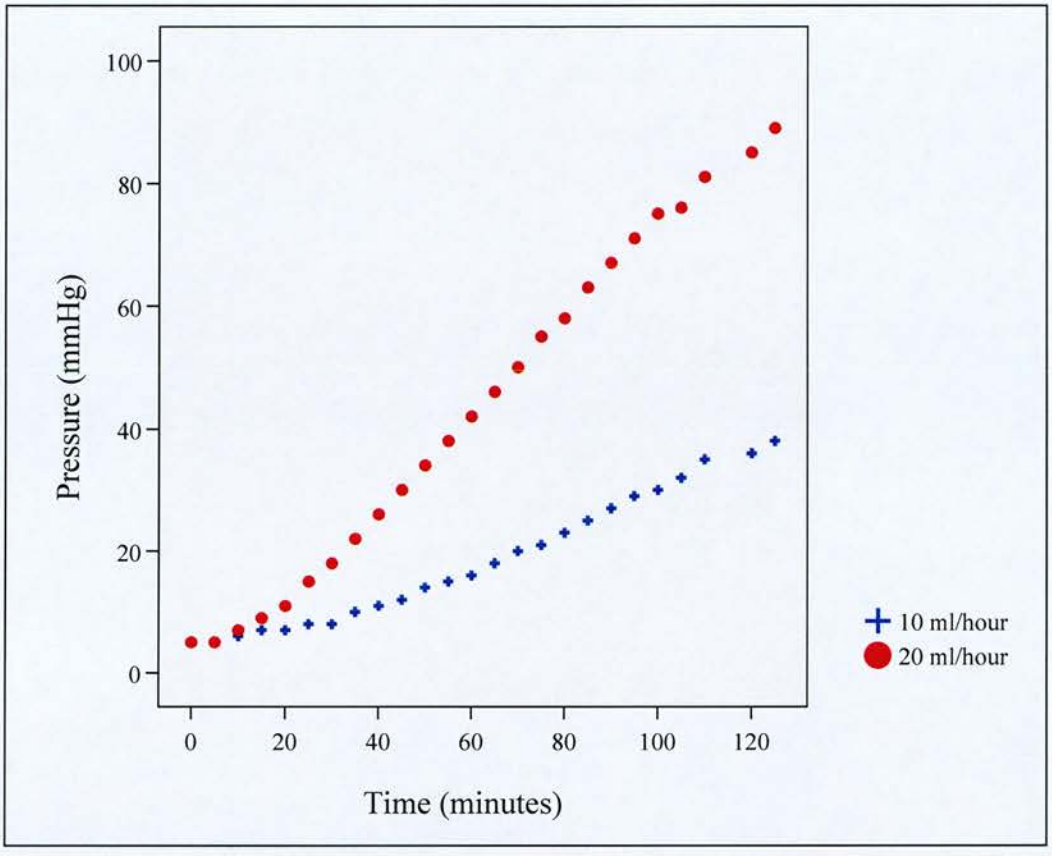

Figure 32 Infusion of saline into 100 ml bag. Change in pressure (mmHg) for two infusion rates, 10ml/hour and 20 ml/hour recorded over 120 minutes.

To establish a true control limb on each animal, an 18-gauge catheter, but no infusion, was placed in the unaffected (left) anterior compartment in the same position to the compartment syndrome leg.

A sub-cutaneous haematoma was required in animals from group two. These were created in legs on both sides by infiltrating 25 ml over five minutes beneath the skin over the anterior compartment at the site corresponding to the tip of the invasive catheter. The 25 ml of blood was drawn from blood that had been stored overnight in 'out of date' blood transfusion bags (supplied by the Blood Transfusion Service, Royal Infirmary of

Edinburgh). Non-invasive StO_2 measurements were taken over the site of the sub-cutaneous haematoma.

The viability of the neuromuscular unit was indicated by the muscle twitch and associated dorsiflexion twitch of the 'ankle'. The loss of the twitch then served as the indicator for the development of an acute compartment syndrome in the anterior tibial muscle compartment (Garr *et al.,* 1999; Arbabi *et al.*, 1999). The twitch from the neuromuscular unit was provided by a nerve stimulator (Stimuplex® Dig RC, B.Braun Hospital Care, Melsungen, Germany) that was placed on the extra-compartmental portion of the lateral fibula nerve on both hind limbs. The stimulator was able to provide a muscle twitch at 0.2 mA. The nerve stimulator was sutured in position. Loss of twitch occurred for two reasons; firstly, due to poor neuromuscular function as a result of the increasing intracompartmental pressure and secondly, due to displacement of the stimulator tip. The former was confirmed by increasing the stimulator current, which then did not create a twitch. This was in contrast to the latter where by increasing the amplitude of the stimulator current and repositioning of the stimulator tip nearer the nerve, the twitch was regained and the current could be returned to 0.2mA. A nerve stimulator was placed also in the left, unaffected leg and the lateral fibula nerve stimulated. This allowed the unaffected leg to be carrying out the same 'work' as the compartment syndrome leg and also provided a control for the determination of the loss of twitch on the compartment syndrome side.

When the compartment syndrome had been induced, the rate of infusion was stopped or reduced so that the compartment pressure was maintained at a constant value for 30 minutes. At the end of this period, fasciotomies were carried out over the anterior compartments on each rear leg. The data collection continued for 30 minutes following the fasciotomies. Observations were made for the presence of subcutaneous and intra-

compartmental haematomas at the time of the fasciotomy. Any evidence of muscle swelling, discoloration, loss of twitch, or reduced bleeding was recorded.

Ultrasound measurements

On each animal, the anterior compartments were examined using a portable ultrasound scanner, the same device that was used in the clinical study (Sonosite^{TM} 180, Sonosite Inc., Bothel, Washington, USA; supplied by Medical Supplies (UK) Ltd.). The purpose of the scanning was to determine the distance between the skin surface and the deep fascia, the depth of the muscle compartment and to establish that the catheters were lying in the correct position.

Ultrasound measurements were taken from the mid-point of the anterior compartment. These were made at two different times during the experimental procedure. Firstly, during the immediate period after completion of the experimental set-up, and secondly when the compartment syndrome had developed. In group 2 animals, measurements were also made following the formation of the sub-cutaneous haematoma. Measurements were made on both hind limbs.

Skin and adipose layer contribution to StO_2 values.

In addition to the compartment syndrome model, the animal study allowed data to be obtained that could assist in the interpretation of the StO_2 values over muscle compartments and understanding of the possible contribution from overlying tissues. The effect of the overlying subcutaneous tissue on StO_2 measurements was investigated after the 30 minute observation period following the fasciotomies had been completed. The experiment to examine the contribution the subcutaneous tissue was carried out only in the normal legs of pigs from group 1 (compartment syndrome induced by plasma infusion).

A reading of StO_2 was initially taken over the anterior compartment with the interface placed on the skin. An area the size of the interface, comprising skin and subcutaneous tissue superficial to the deep fascia, was dissected free of any attachments so that the tissue became ischaemic. This ischaemic 'patch' was created so that it could be replaced over the underlying muscle. A cut down to the ipsilateral common femoral artery was then made so that the vessel could be clamped to obstruct arterial inflow to the hind limb. The arterial clamp was applied for 15 minutes to induce ischaemia. StO_2 values were recorded over the following combinations:

1. **Normal subcutaneous tissue and muscle**
2. **Ischaemic subcutaneous tissue and normal muscle**
3. **Normal muscle alone**
4. **Ischaemic muscle alone**
5. **Ischaemic subcutaneous tissue and ischaemic muscle**

The distance from skin surface to deep fascia was measured and recorded.

StO_2 measurements at 25mm and 12mm.

Alongside isolating the skin and subcutaneous tissue by dissection, it was possible to examine the StO_2 in the superficial layers using a NIRS interface that recorded only from the superficial 12 mm of tissue. This equipment only became available during the animal study and so was applied to three animals in groups 1 and 3 and to four animals in the sub-cutaneous haematoma group (group 2).

Preparation of Compartment Infusions

The first experiment to be carried out was from group 3 so that 100mls of blood was withdrawn from the carotid artery and placed into a transfusion bag, before being drawn up into a syringe for the intra-muscular infusion. Immediately before the

anaesthetic was terminated for each animal, arterial blood was collected via the cut down to the common carotid artery and stored in standard 'out of date' blood transfusion packs (Blood Transfusion Service, Edinburgh). The volume of blood collected was 300 ml for each collection. The blood was stored at 4°C until the following experiment. When it was required, it was removed from the fridge at 0730 hrs so that it could equilibrate with room temperature. It was not attempted to bring the blood up to body temperature prior to infusion in view of the fact that the infusion was slow and via a thin infusion line. If the blood was required as whole blood then the bags could be gently agitated so that the blood constituents were mixed. When plasma was required the supernatant was aspirated directly through the side of the bag and could be used directly for infusion into the compartment. This procedure avoided the need for additional sedation of the animal and venepuncture before each experiment.

Following collection of blood for infusions, each animal was killed. Application for killing by a non-schedule 1 method (bleeding-out) was made in addition to a schedule 1 method. (Animals (Scientific Procedures) Act 1986).

Statistical analysis

Statistical analysis was performed to assess the degree of correlation between the non-invasive StO_2 measurements provided by the InSpectra™ Tissue Spectrometer and the pressures obtained from within the compartments during the induction and release of the acute compartment syndrome. The data obtained from the invasive pH, pO_2 and pCO_2 monitor was also assessed for correlation with both non-invasive StO_2 and compartment pressure measurements.

3.3 Results

The animal study was carried out between September and December 2001. There were no unexpected animal deaths during the procedures. Table 22 demonstrates baseline recordings for the animals in the three groups. There were no significant differences between the animals in the three groups. A comparison of the initial and final (pre-fasciotomy) blood gas analyses has been made in Table 23.

Animal model group	**Mass (kg) (± SD)**	**Central temp.(^{o}C) (± SD)**	**Systolic blood pressure (mmHg) (± SD)**	**Diastolic blood pressure (mmHg) (± SD)**	**Pulse (bpm) (± SD)**	**Oxygen saturation (%)(± SD)**
1.Plasma infusion only	108(± 19)	35.6 (± 1.2)	94 (± 19)	53 (± 6)	104 (± 21)	98 (± 0.5)
2.SC haematoma	106 (± 24)	36.6 (± 0.6)	98 (± 20)	47 (± 9)	108 (± 22)	98 (± 0.6)
3 Intra-muscular infusion	101 (± 17)	35.4 (± 2.0)	101 (± 24)	49 (± 6)	108 (± 25)	98 (± 1.0)

Table 22 Baseline parameters for the three animal model groups. There was no significant difference between groups for any parameters. (independent samples T-test)

Value	Initial ABG sample (± SD)	Pre-fasciotomy ABG sample (± SD)	Significance
pH	7.21 (± 0.04)	7.15 (± 0.06)	$p < 0.01$
pCO_2 (mmHg)	85 (± 10)	107 (± 17)	$p < 0.01$
pO_2(mmHg)	311 (± 63)	252 (± 75)	$p = 0.03$
HCO_3 (mmHg)	33 (± 2)	36 (± 2)	$p < 0.01$
Base excess (mmol/l)	5.1 (± 2.0)	5.6 (± 1.9)	$p = 0.4$
Sodium (mmol/l)	146 (± 1)	145 (± 2)	$p = 0.1$
Potassium (mmol/l)	3.6 (± 0.3)	5.6 (± 1.1)	$p < 0.01$
Haemoglobin (g/dl)	7.7 (± 0.8)	9.5 (± 2.7)	$p = 0.02$
Haematocrit (%)	23 (± 2)	28 (± 8)	$p = 0.02$

Table 23 Arterial blood gas parameters for the three animal model groups, analysed collectively to look at changes over the duration of the experiments (mean time 231 min. ± 28).

The analysis of the arterial blood gas parameters demonstrates significant changes during the course of the experiments for animals in all groups. The changes were highly significant with regard to pH, pCO_2, and HCO_3 and potassium levels. The only significant differences that were found between the groups were of a decrease in pO_2 when the initial and pre-fasciotomy values of the plasma infusion group were compared with the animals in the subcutaneous haematoma group (Figure 33). The initial mean pO_2 values for groups 1 and 2 were 341 mmHg and 263 mmHg ($p = 0.06$) and the pre-fasciotomy mean values were 282 mmHg and 197 mmHg ($p = 0.03$). The initial mean saturations were 100% and 99.6% ($p = 0.1$) for groups one and two respectively, and the pre-fasciotomy mean values were 99.8% and 98.8% ($p < 0.01$).

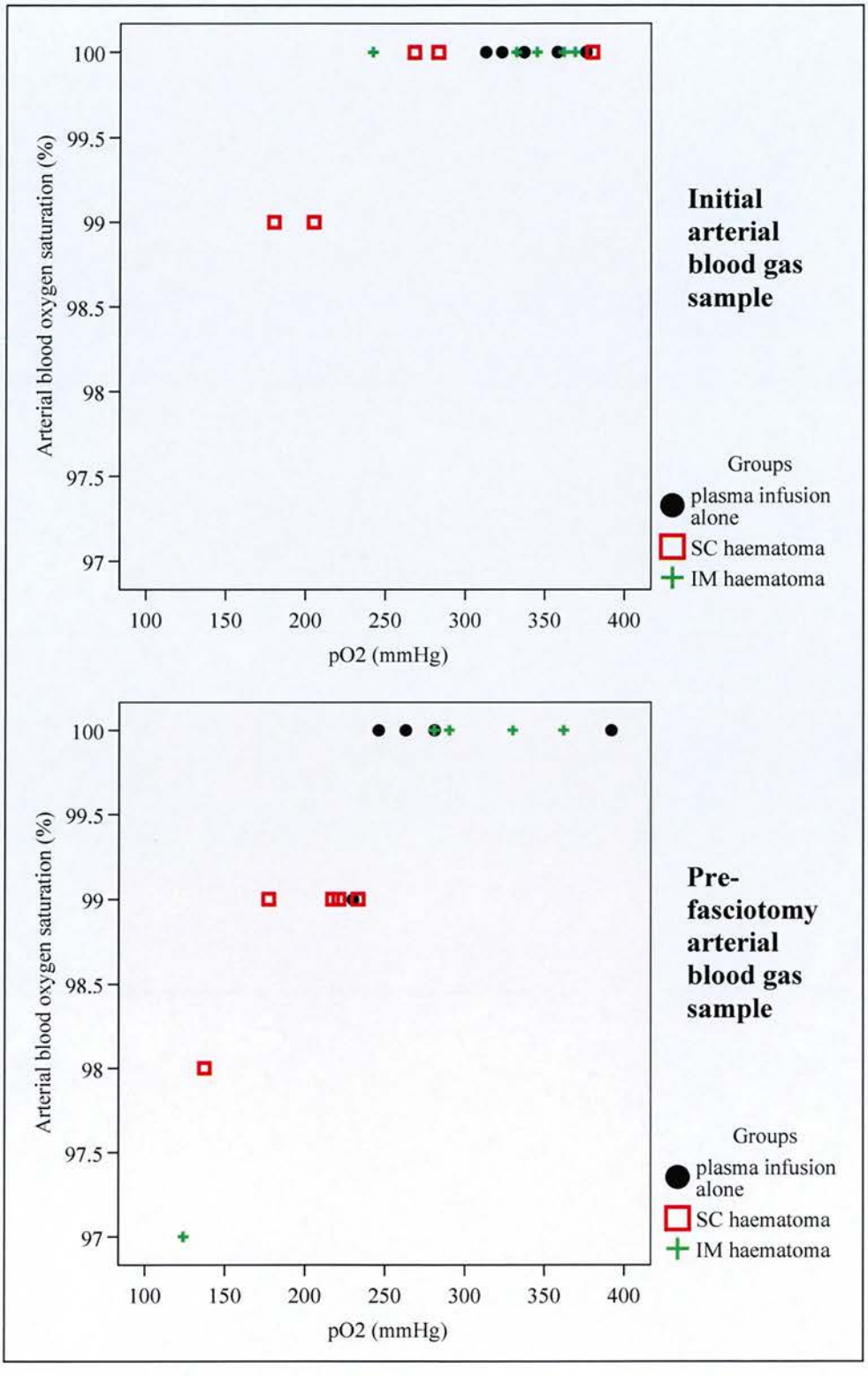

Figure 33 Initial and pre-fasciotomy arterial blood gas samples, demonstrating reduction in arterial blood pO_2 and saturation ($p = 0.03$ and $p < 0.01$) in animals in group 2 (plasma infusion with subcutaneous haematoma)

Induction of Acute Compartment Syndrome

The infusions of either plasma or whole blood into the muscle compartments were completed without difficulty. The mean total volume (± SD) infused for the three groups up to the point of loss of muscle twitch was 51.8 ml (± 9), 48.6 ml (± 9) and 55.9 ml (± 7) respectively. There was no statistical significance between the groups. The value for the subcutaneous haematoma (group 2) was slightly less as the effect of the subcutaneous haematoma lying outside the fascia may have contributed to the overall increase in pressure within the compartment. The mean time (± SD) from the start of the infusion to the loss of muscle twitch was 168 min (± 35), 147 min (± 29) and 170 min (± 10) for the three groups. No statistically significant difference between the groups was observed. The subcutaneous haematoma and plasma infusion group (group 2) displayed a shorter time to loss of twitch than the other two groups, again possibly due to the added effect of having 25 ml of blood beneath the skin as well as the effect of the plasma infusion within the muscle compartment. The mean total lengths of time (± SD) from the beginning of the experiment to the loss of twitch, when the second arterial blood gas was taken, were 184 min (± 31), 196 min (± 31) and 189 min (± 15) for the three groups. There was no statistical significance between the groups. When the total time to loss of twitch is examined, the subcutaneous haematoma group (group 2) is slightly longer. This is due to an additional time (15 min) at the beginning of the procedure when the subcutaneous haematoma in this group was being added. The overall increase in length of experimental time for animals from group 2 could account for the larger drop in systemic oxygen saturation and pO_2 with respect to the other groups over the total length of the experiments.

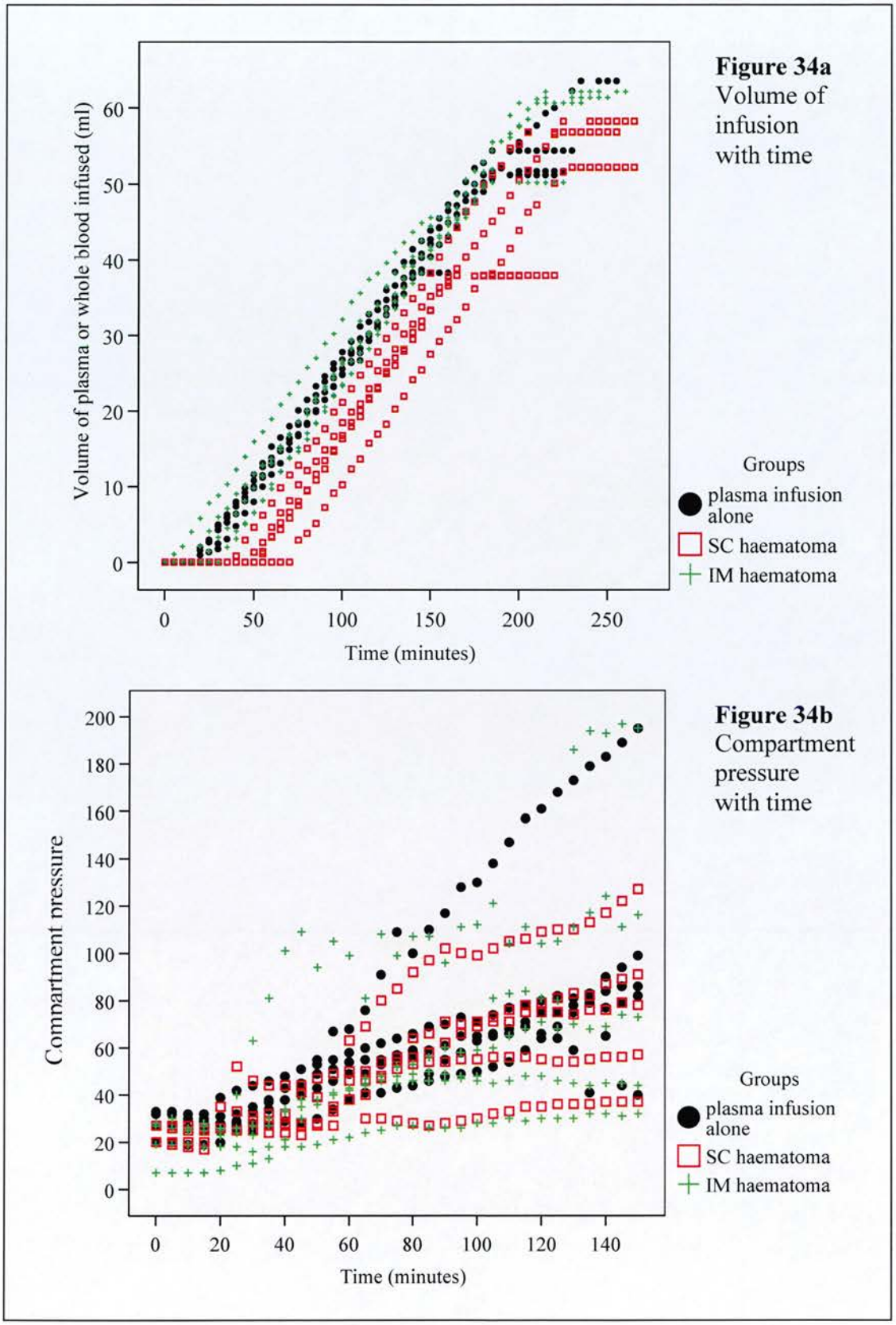

Figure 34a Volume of infusion with time

Figure 34b Compartment pressure with time

Figure 34a Volume of infusion (ml) with time for the three experimental groups (plasma infusion alone, subcutaneous haematoma and plasma infusion and intramuscular infusion of whole blood).

Figure 34b Compartment pressure (mmHg) with time over the first 150 minutes for the three experimental groups.

Figure 34a demonstrates the change in volume of infusion plotted against time for the three groups. The resultant rise in pressure is steady for the majority of animals (Figure 34b). A steeper rise in pressure was seen in one animal from each of groups 1 and 2 and in two animals from group 3. The volume infused was found to correlate closely with the compartment pressure (correlation = 0.6, $p < 0.01$).

Compartment Monitoring

Compartment pressures from the anterior leg compartment were recorded in the 'compartment syndrome' leg and the normal side in all animals. The mean initial resting pressures for the compartment syndrome leg of the three groups respectively were as follows (± SD): 29 mmHg (± 5.4), 24 mmHg (± 3.8) and 22 mmHg (± 9.0). There was no significant difference between the groups. Following the infiltration of 25 ml of blood to create the subcutaneous haematoma in animals in group 2, the resting pressure increased to a mean of 34 mmHg.

The mean pressures for the thirty-minute period following the loss of twitch and prior to the fasciotomy were calculated (Table 24). The mean compartment pressures from the 'compartment syndrome' legs had a range from 78 mmHg to 106 mmHg. The mean compartment pressures from the normal side ranged from 16 mmHg to 23 mmHg. There was no statistical significant difference between the compartment pressure measurements for the three groups. The resting pressure on the normal legs was higher than expected compared to the resting pressures in humans where approximately 5 mmHg would be expected (Mubarak *et al.,* 1976).

		Group 1. Plasma infusion alone		Group 2. SC haematoma and plasma infusion		Group 3[a]. Intramuscular infusion of blood	
		Mean value (± SD)	Significance (between groups 1 and 2)	Mean value (± SD)	Significance (between groups 2 and 3)	Mean value (± SD)	Significance (between groups 1 and 3)
Compartment pressure ACS leg (mmHg)		**106** (± 55)	p = 0.3	**78** (± 27)	p = 0.7	**95** (± 73)	p = 0.8
Compartment pressure norm leg (mmHg)		**23** (± 9)	p = 0.4	**19** (± 5)	p = 0.3	**16** (± 1)	p = 0.2
ΔP (mmHg) compartment syndrome leg		**-54** (± 50)	p = 0.4	**-31** (± 29)	p = 0.7	**-45** (± 75)	p = 0.8
StO_2 over 25mm depth from skin surface (%)	**compartment syndrome leg**	**12** (± 10)	p < 0.01	**77** (± 19)	p < 0.01	**11** (± 9)	p = 0.8
	normal leg	**71** (± 17)	p = 0.2	**84** (± 11)	p = 0.2	**76** (± 7)	p = 0.5
	StO_2 difference	**-56** (± 16)	p < 0.01	**-1** (± 18)	p < 0.01	**-64** (± 14)	p = 0.4
StO_2 over 12mm depth from skin surface (%)	**compartment syndrome leg**	**44** (± 15)	p < 0.01	**84** (± 13)	p = 0.1	**38** (± 19)	p = 0.8
	normal leg	**76** (± 3)	p = 0.04	**85** (± 18)	p = 0.7	**80** (± 8)	p = 0.6
	StO_2 difference	**-32** (± 13)	p < 0.01	**-1** (± 5)	p = 0.3	**-42** (±27)	p = 0.7

Table 24 Mean values for 30 minute period after loss of twitch and before fasciotomy. Compartment pressure and StO_2 measurements (25 mm and 12 mm) for compartment syndrome and normal legs divided by the three experimental groups (plasma infusion alone, SC haematoma and plasma infusion and IM infusion of blood). Independent samples t-test. [a] - Animal 10 excluded.

The initial pressures in the normal legs were slightly higher than the final pressures (25 mmHg, 20 mmHg and 21 mmHg for the three groups respectively) and reflect the process of flushing the catheter with 1.0 ml of saline after insertion to ensure an intact column of saline. The fall in pressures in the normal leg for all groups indicates that the extended position of the rear leg in the pig did not itself precipitate a possible 'well-leg' compartment syndrome (Tan *et al.*, 2000).

Near-infrared spectrometer measurements were carried out on both legs over the mid-point of the anterior compartment using two interfaces. The first, as used in the clinical study, sampled between the skin surface and 25mm in depth, the second, sampled between the skin surface and 12 mm in depth. Before the remainder of the results are analysed, the results for the StO_2 over 25 mm for animal 10 in the intramuscular group are examined separately as they did not appear to fit with the other animals in the group (Figure 35). When the fasciotomy was carried out for this animal, it was found that there was blood lying in the sub-cutaneous tissues that had leaked from the intra-muscular infusion of whole blood (Figure 36). The results for animal 10 were similar to that of the sub-cutaneous haematoma animals. In view of the leakage of blood outside the muscle compartment, animal 10 was not included in further analysis.

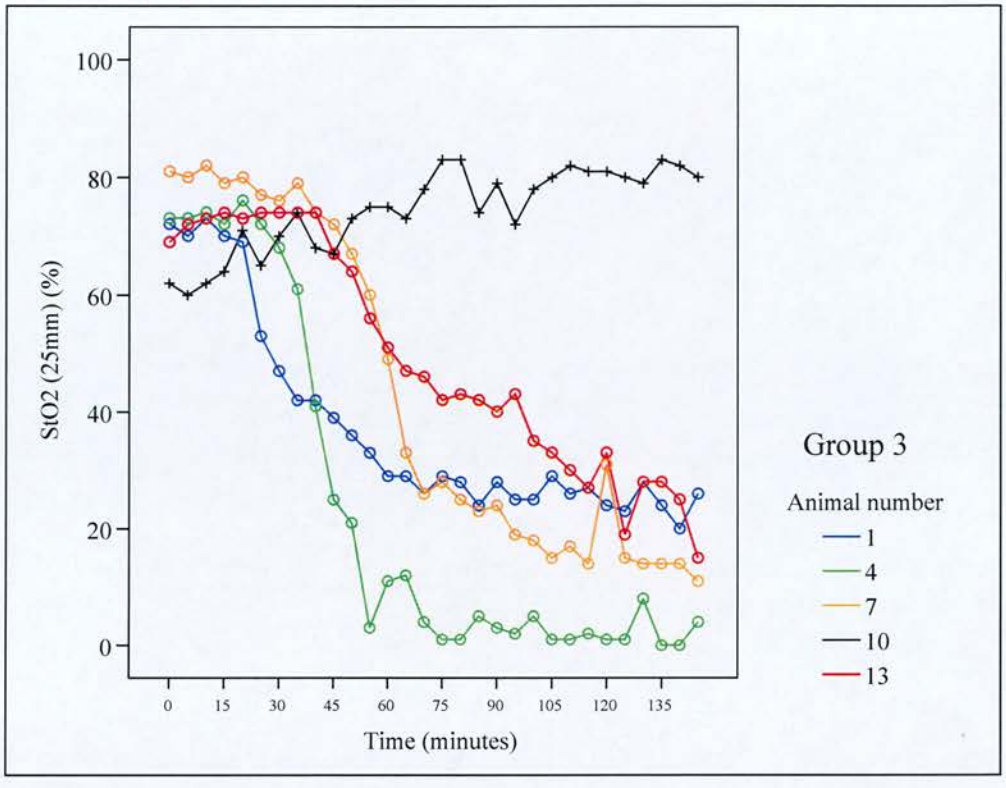

Figure 35 StO_2 (25mm) (%) for the IM haematoma group (group 3) over the first 150 min of experiment. Animal 10 (black line with crosses) appeared as an outlier and at fasciotomy, blood in the sub-cutaneous tissue was found (Figure 33).

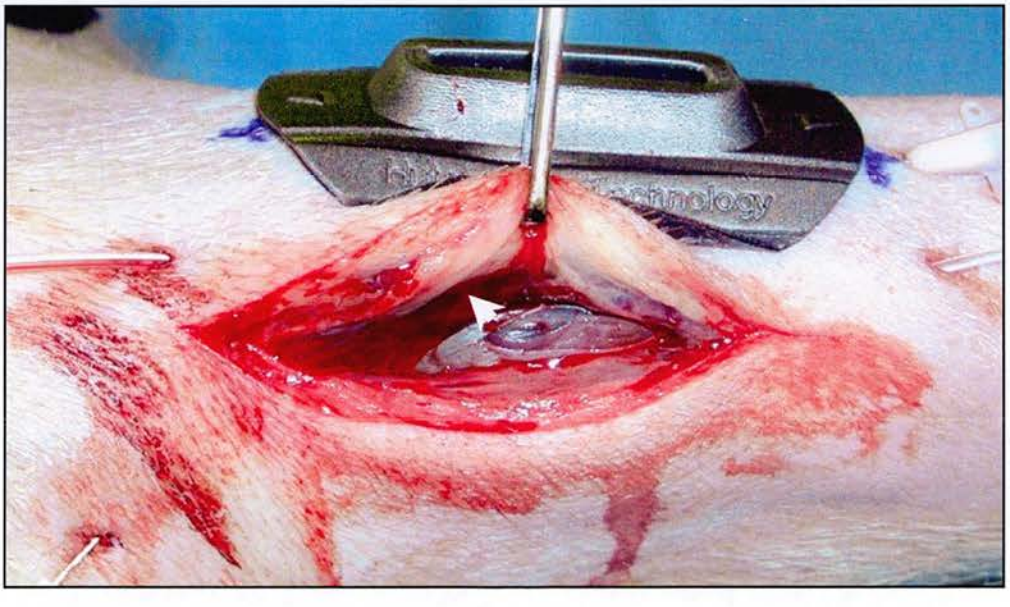

Figure 36 Photograph of lateral fasciotomy of compartment syndrome side of animal 10. A collection of blood was visible lying outside the deep fascia of the anterior compartment (arrow).

Examination of the 'compartment syndrome' leg revealed that the mean StO_2 (25mm) at the loss of twitch in animals in groups 1 and 3 fell to 12% (± 10) and 11% (± 9) respectively. This was in contrast to the mean StO_2 at the loss of twitch in the animals where there had been a subcutaneous haematoma and plasma infusion (group 2) where the value was 77% (± 19). This value was highly significant compared to both other groups (Table 24). In order to account for any inter-animal variation, the StO_2 difference has been calculated, as in the clinical study, by subtracting the StO_2 on the normal side from that on the compartment syndrome side. The mean StO_2 difference (25 mm) (± SD) for groups 1 and 3 was –56% (± 16) and –64% (± 14) respectively. The mean StO_2 difference (25 mm) for the SC haematoma group (group 2) was –1% (± 18) ($p < 0.01$). As the fasciotomies have occurred at different times, the three groups have been compared graphically over the first 150 minutes of the experiments (Figures 37 –41). Later analysis examines the periods immediately before and after the fasciotomy.

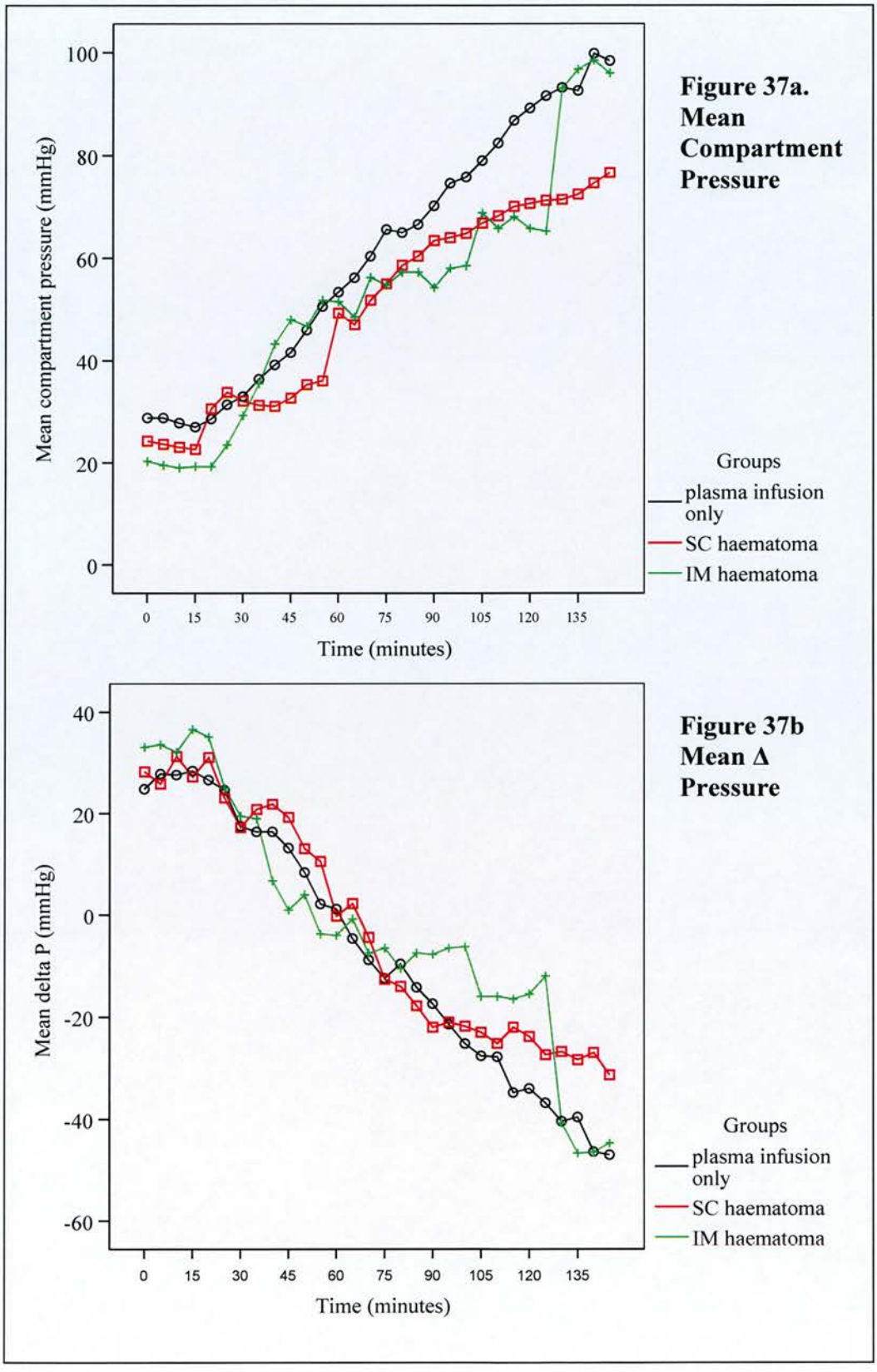

Figure 37 Mean compartment pressures (mmHg) and Mean Δ pressure (mmHg) for the three experimental groups over the first 150 minutes (pre-fasciotomy).

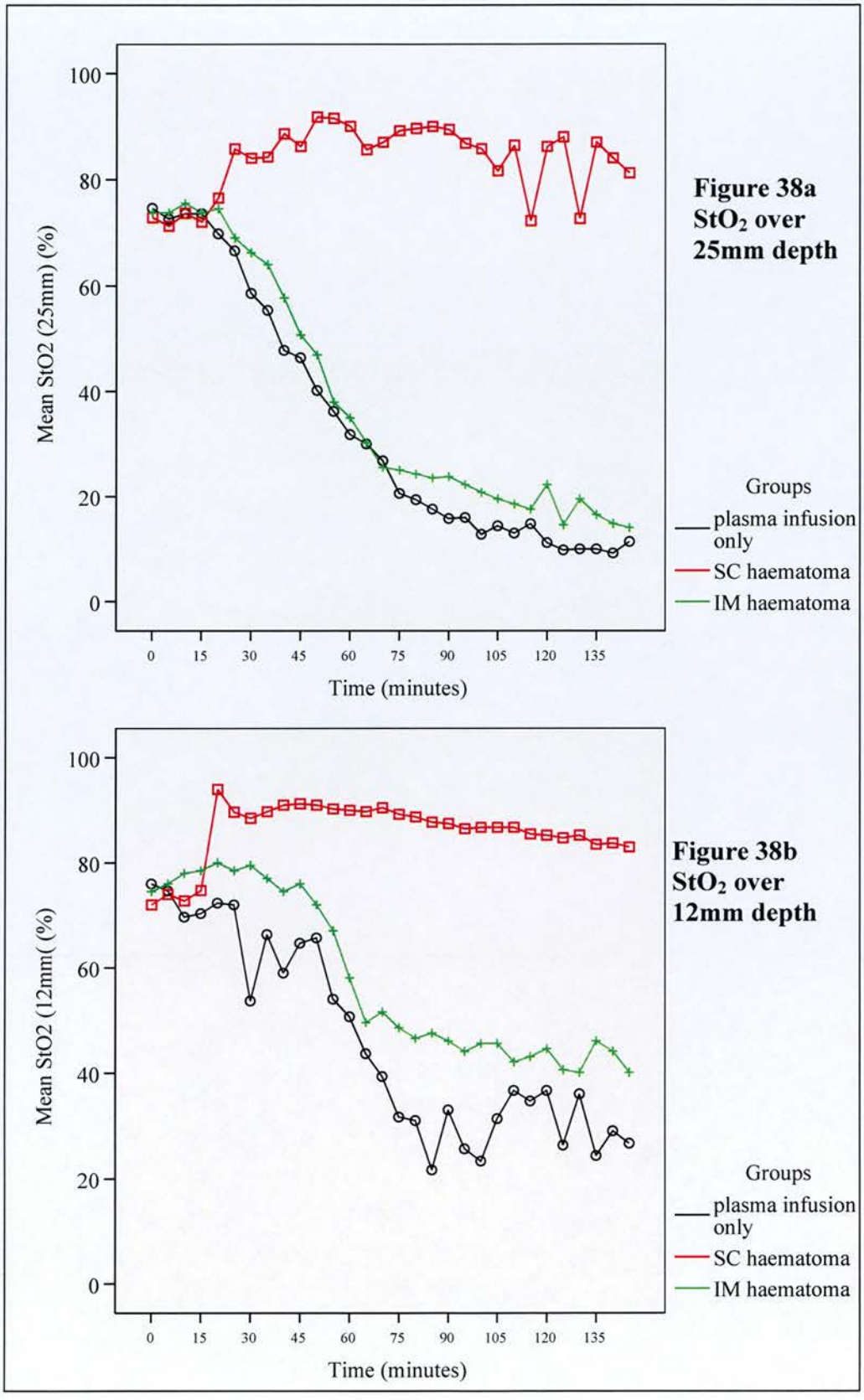

Figure 38 Mean StO_2 values at 25 mm and 12 mm depths for the three experimental groups over the first 150 minutes (pre-fasciotomy)

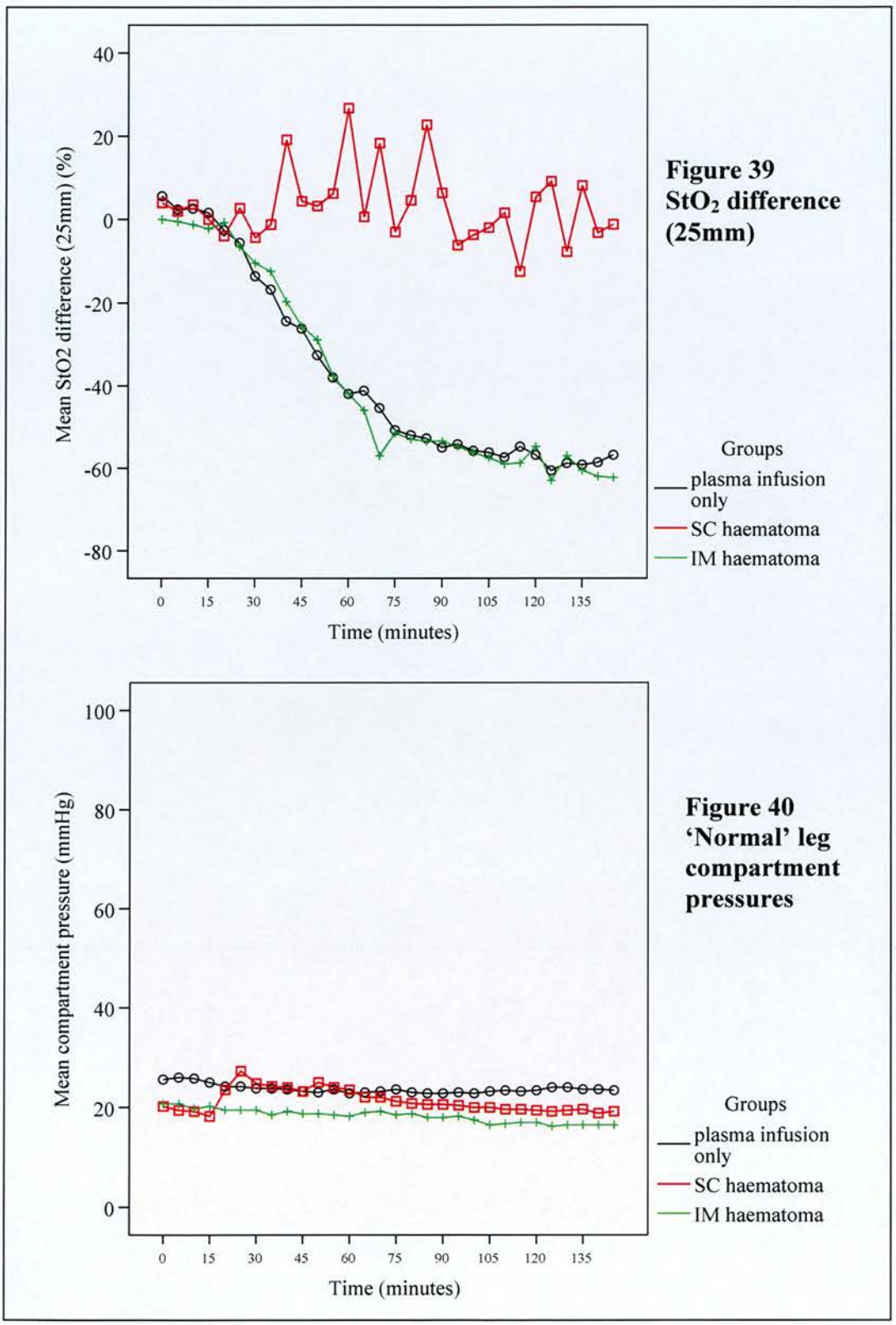

Figure 39 StO_2 difference (25mm)

Figure 40 'Normal' leg compartment pressures

Figure 39 Mean StO_2 difference over 25mm depth for the three experimental groups over the first 150 minutes of experimental procedure. Wider variation is seen in the SC haematoma group

Figure 40 Mean compartment pressures (mmHg) in 'normal' legs. Note the rise in pressure when the SC haematoma was introduced (group 2).

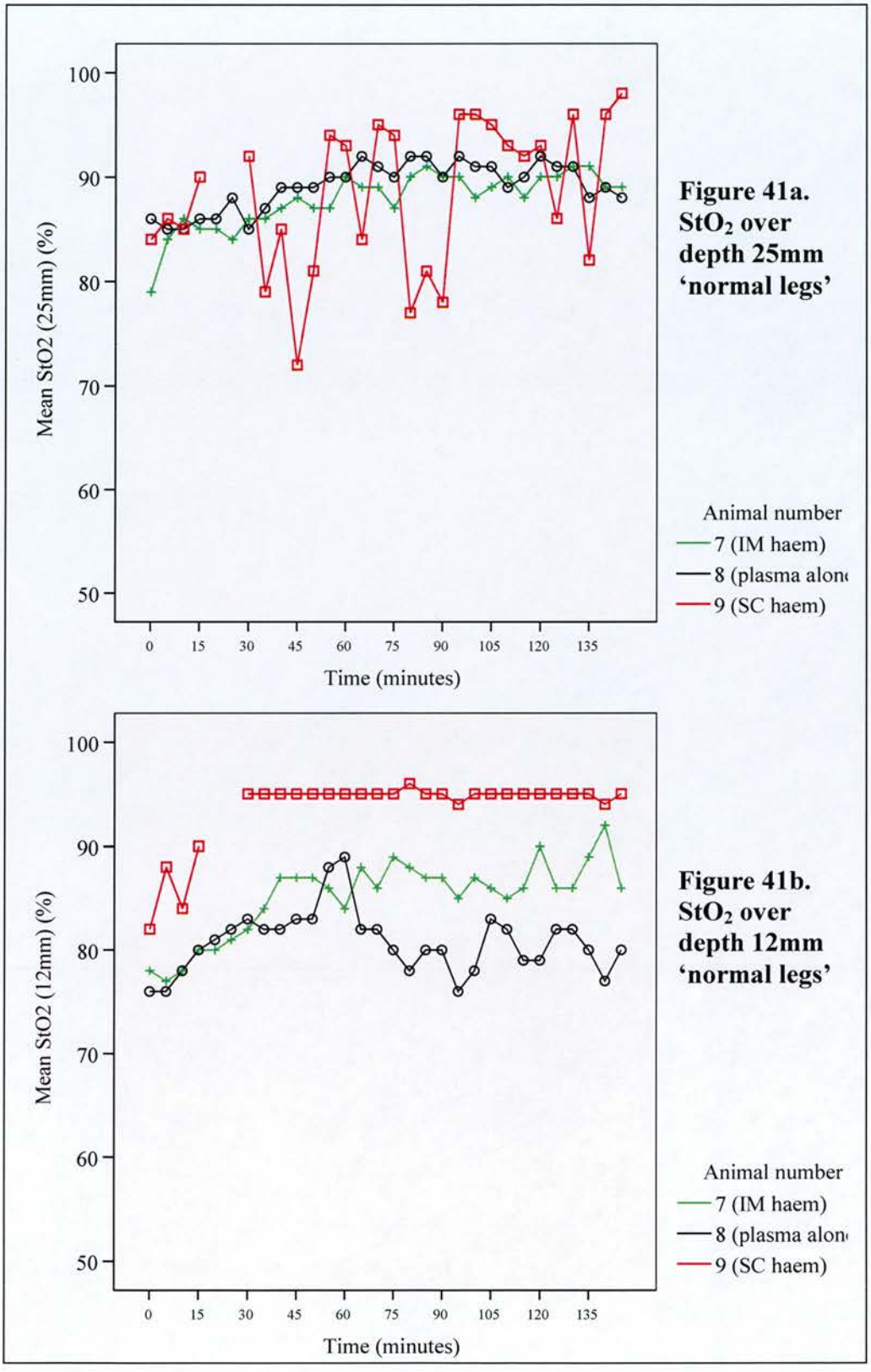

Figure 41 StO_2 values for individual animals from the three different groups at 25 mm (Fig 41a) and at 12 mm (Fig 41b). Note the StO_2 scale 50 – 100% only shown. The different effect of the subcutaneous haematoma on the 25 mm and 12 mm values is demonstrated.

Measurements of StO_2 between the skin surface and 12 mm in depth were reduced similarly in groups 1 and 3; mean values (± SD) at the loss of twitch were 44% (± 15) and 38% (± 19) respectively (table 24). The mean StO_2 (12mm) for animals with a subcutaneous haematoma and plasma infusion (group 2) in the pre-fasciotomy period was 84% (± 13). There was a highly significant difference between groups 1 and 2, but the difference between groups 2 and 3 did not reach statistical significance ($p = 0.6$).

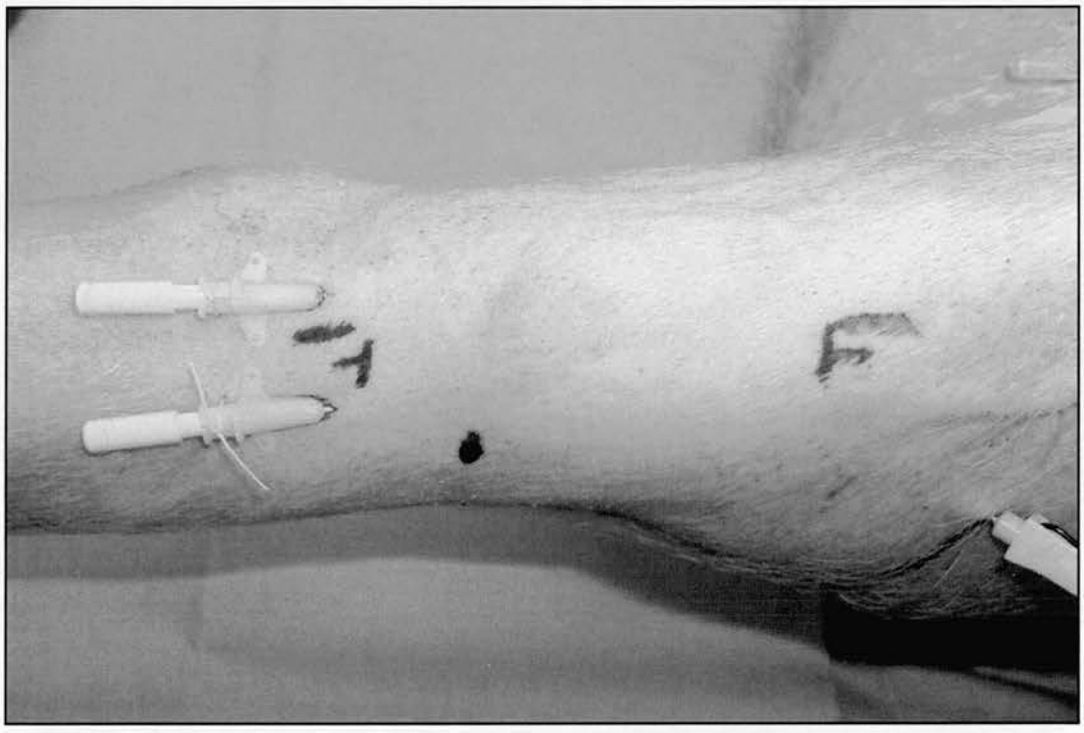

Figure 42 Photograph of the non-compartment syndrome leg of animal 15 (group 2) following the injection of 25 ml blood into the subcutaneous tissues over the anterior compartment. Only slight discolouration in the superficial tissue can be seen. 'Dummy' catheters have been inserted as this is a control side.

The 'normal' legs in animals from group 2 also had a sub-cutaneous haematoma, but no infusion so that the effect of the sub-cutaneous haematoma alone could be established (Figure 42). Comparison of the StO_2 values before and after the addition of the sub-cutaneous haematoma revealed a highly significant increase (Table 25). This increase was greater for the StO_2 measured from the superficial 12 mm compared to the value recorded over 25 mm. Analysis of mean values in the figures above hide some of the changes to the variability that was seen following the addition of the subcutaneous haematoma. StO_2 measured over 25 mm appeared to fluctuate widely with the addition of the subcutaneous haematoma compared to the other groups, but at 12 mm the effect of the addition of the subcutaneous haematoma on the StO_2 of was the opposite, the readings became steadier. Figures 41a and 41b show data from individual animals (numbers 7, 8 and 9) rather than mean values and therefore demonstrate the differences more clearly.

		Mean StO_2 (%) (± SD)	**Significance**
Using 25mm interface	before SC haematoma	**71** (± 10)	$p < 0.01$
	after SC haematoma	**84** (± 10)	
Using 12mm interface	before SC haematoma	**72** (± 19)	$p < 0.01$
	after SC haematoma	**87** (± 12)	

Table 25 Mean StO_2 (%) over 25mm depth and 12mm depth before and after the addition of 25 ml blood into the subcutaneous tissue of normal legs, of animals in group 2.

Figures 37a, 37b and 40 demonstrate that all three experimental groups were subjected to similar pressure changes. A slight pressure rise is noted in the subcutaneous haematoma group (group 2) with the addition of the haematoma at 15 minutes in both the compartment syndrome and 'normal' legs. The differences between groups with regard to the StO_2 values in Table 23 are clearly demonstrated graphically in Figures 35a, 35b and 36. StO_2 measured over the 25 mm depth fell rapidly initially before reaching a steady state. This pattern was not seen in animals from group 2 with the subcutaneous haematoma was overlying the muscle compartment with the plasma infusion. In these animals the StO_2 rose after the injection of 25 ml whole blood into the subcutaneous tissue and the level remained above the resting StO_2 despite increasing pressure. This effect was seen both over the superficial 12 mm and over 25 mm of tissue and in both the compartment syndrome legs and 'normal' legs (Table 25). There was no significant difference between the anterior compartment infused with whole blood (intramuscular haematoma – group 3) and that of the plasma infusion only (group 1) compartments (Table 24).

The pre-fasciotomy and post fasciotomy periods have been analysed from the loss of twitch until the end of the procedures. It was not possible to accurately compare the experiments over the whole duration as the timing of the fasciotomy was dictated by the loss of twitch rather than a fixed time point. The compartment pressure reduction between the thirty-minute period before fasciotomy, *i.e.* after the loss of twitch, and the period after fasciotomy was significant in all groups in both legs (Figure 43a, Table 26). There were no significant differences in compartment pressure between the groups in both legs during the post-fasciotomy period.

Following the fasciotomy, there were highly significant increases in StO_2 at 12 mm and 25 mm for animals from group 1 (plasma infusion only) on the compartment

syndrome side. For the 'normal' side in group 1 the StO_2 also increased. This was highly significant for StO_2 at 12 mm. In contrast, group 2 (sub-cutaneous haematoma and plasma infusion) did not show any significant changes following the fasciotomy with regard to StO_2 at 12 and 25 mm (Table 26). In group 2 the levels remained elevated as they had been in the pre-fasciotomy period.

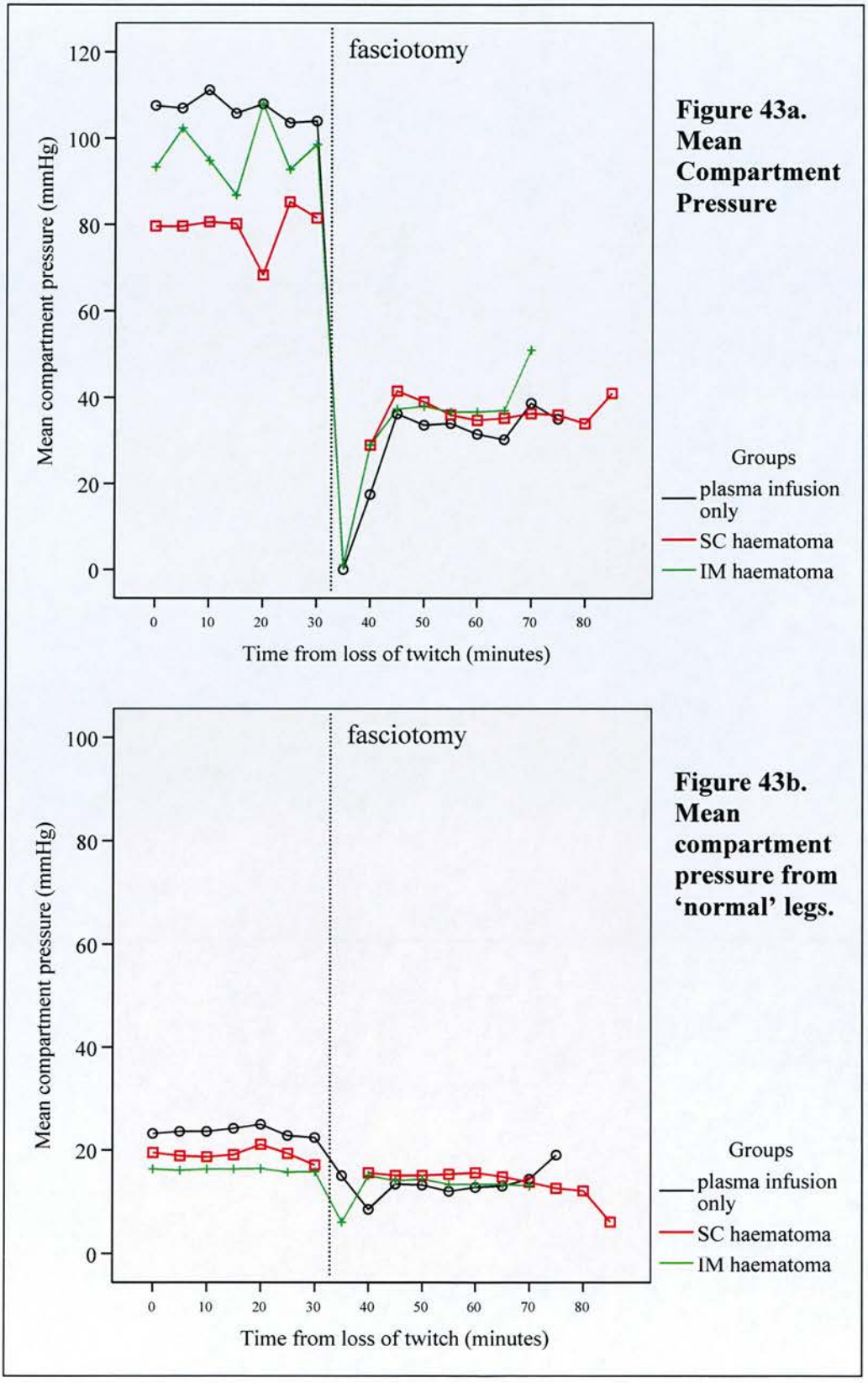

Figure 43a. Mean Compartment Pressure

Figure 43b. Mean compartment pressure from 'normal' legs.

Figures 43 Mean compartment pressures (mmHg) from compartment syndrome and 'normal' legs for the three experimental groups 30 min before and after fasciotomy.

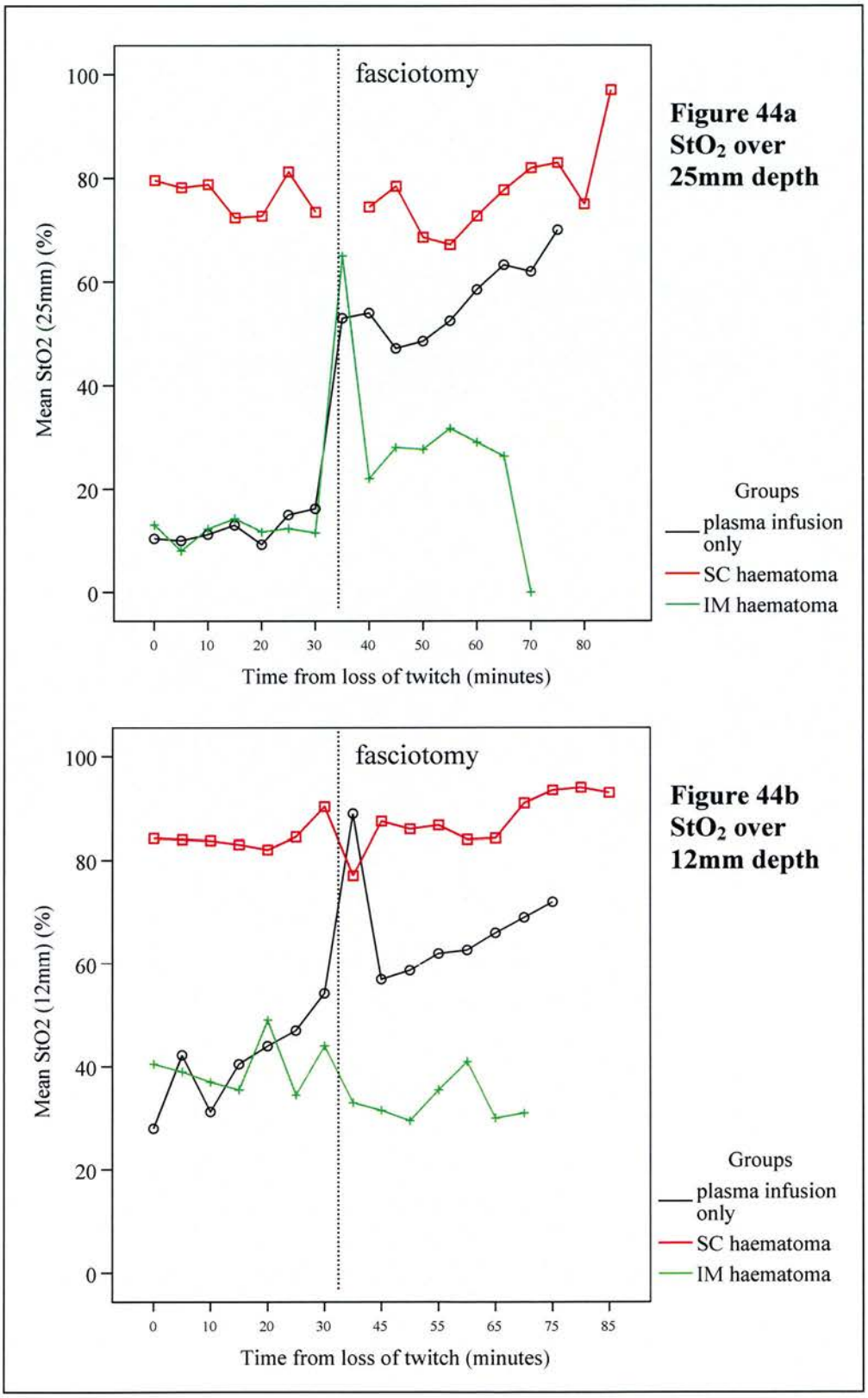

Figure 44 Mean StO_2 values at 25 mm and 12 mm depths for the three experimental groups, time from loss of twitch (minutes). Fasciotomy carried out at 30 min from loss of twitch.

		Group 1. Plasma infusion alone		Group 2. SC haematoma and plasma infusion		Group 3[a]. Intramuscular infusion of blood	
		Mean difference (± SEM)	**Significance**	**Mean difference (± SEM)**	**Significance**	**Mean difference (± SEM)**	**Significance**
Compartment pressure ACS leg (mmHg)		**-75** (± 9)	$p < 0.01$	**-42** (± 5)	$p < 0.01$	**-60** (± 13)	$p < 0.01$
Compartment pressure norm leg (mmHg)		**-10** (± 2)	$p < 0.01$	**-4** (± 1)	$p < 0.01$	**-3** (± 1)	$p < 0.01$
ΔP (mmHg) compartment syndrome leg		**73** (± 9)	$p < 0.01$	**39** (± 5)	$p < 0.01$	**59** (± 14)	$p < 0.01$
StO_2 over 25mm depth from skin surface (%)	**compartment syndrome leg**	**42** (± 3)	$p < 0.01$	**-1** (± 5)	$p = 0.8$	**17** (± 8)	$p = 0.02$
	normal leg	**5** (± 3)	$p = 0.2$	**-2** (± 4)	$p = 0.6$	**3** (± 2)	$p = 0.07$
	StO_2 difference	**35** (± 4)	$p < 0.01$	**-3** (± 4)	$p = 0.5$	**13** (± 8)	$p = 0.1$
StO_2 over 12mm depth from skin surface (%)	**compartment syndrome leg**	**22** (± 5)	$p < 0.01$	**3** (± 3)	$p = 0.3$	**-6** (± 5)	$p = 0.2$
	normal leg	**3** (± 1)	$p < 0.01$	**1** (± 4)	$p = 0.8$	**2** (± 2)	$p = 0.5$
	StO_2 difference	**19** (± 5)	$p < 0.01$	**2** (± 1)	$p = 0.2$	**-7** (±6)	$p = 0.2$

Table 26 Mean differences (and standard error of mean difference) between the 30 min period before and after the fasciotomy. Compartment pressures and NIRS measurements displayed. Independent samples t-test. [a] Animal 10 excluded.

The animals from group 3 (intra-muscular infusion of whole blood) had a smaller but significant rise in the mean StO_2 (25mm) depth following the fasciotomy. No significant differences were seen in StO_2 (12mm) or on the 'normal legs' for this group after fasciotomy. Figures 41a and 41b demonstrate that the StO_2 at 12 mm and 25 mm increased in the plasma infusion only group (group1), but not in the other two groups. The rise in StO_2 following the fasciotomy in the plasma infusion only group (group1) compared to the intramuscular group (group 3) was significant where the mean StO_2 (12mm) increased by 30% and StO_2 (25mm) by 26% ($p < 0.01$).

The StO_2 (25mm) depth was found to correlate with the compartment pressure in animals from group 1 and 3, this correlation did not hold for animals from the sub-cutaneous haematoma with plasma infusion group (group 2) (table 27).

		Group 1. Plasma infusion alone		Group 2. SC haematoma and plasma infusion		Group 3[a]. Intramuscular infusion of blood	
		Correl.	**Sig.**	**Correl.**	**Sig.**	**Correl.**	**Sig.**
StO_2 (25mm)	**compartment syndrome leg**	-0.66	$p < 0.01$	0.07	$p = 0.3$	-0.55	$p < 0.01$
	normal leg	0.2	$p < 0.01$	0.22	$p < 0.01$	-0.04	$p = 0.6$
	StO_2 difference	0.75	$p < 0.01$	-0.04	$p = 0.5$	-0.51	$p < 0.01$
StO_2 (12mm)	**compartment syndrome leg**	-0.60	$p < 0.01$	0.32	$p < 0.01$	-0.03	$p = 0.8$
	normal leg	0.11	$p = 0.2$	0.32	$p < 0.01$	-0.3	$p < 0.01$
	StO_2 difference	-0.60	$p < 0.01$	-0.23	$p < 0.01$	0.06	$p = 0.5$

Table 27. Correlation for compartment pressure (from compartment syndrome leg) and StO_2 at 12 and 25 mm for compartment syndrome legs and 'normal' legs and StO_2 difference (calculated). 1.0 = exact correlation, 0.0 = no correlation; [a] Animal 10 excluded.

The correlation between compartment pressure and StO_2 at 12mm for the intra-muscular haematoma (group 3) was not significant. The correlation for StO_2 at 12mm was highly significant in both groups 1 and 2. This was negative in group 1, indicating that a rise in pressure was associated with a fall in the StO_2 value. The inverse was true for animals from group 2.

In order to establish the relationship between StO_2 (25mm) and compartment pressure in this animal model, the raw data for the animals from all groups have been plotted separately (Figure 45 and 46). The mean correlation of linear models for each group have been estimated.

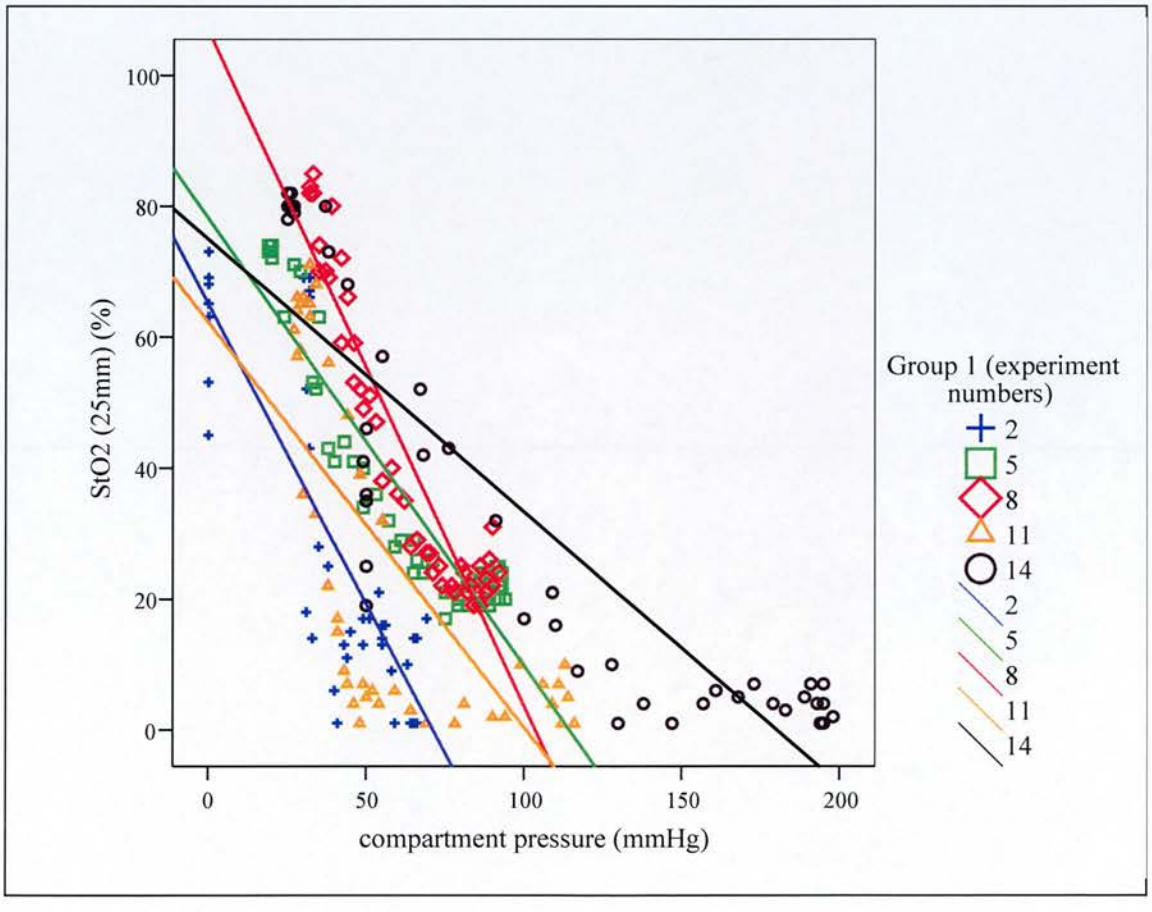

Figure 45a Scatter plots of compartment pressure (mmHg) by StO_2 (25mm) (%) for animals in group 1. Mean correlation coefficient for linear models for group 1 = – 0.7. Correlations between compartment pressure and StO_2 in all animals in Group 1 were significant ($p < 0.01$ Spearman rho).

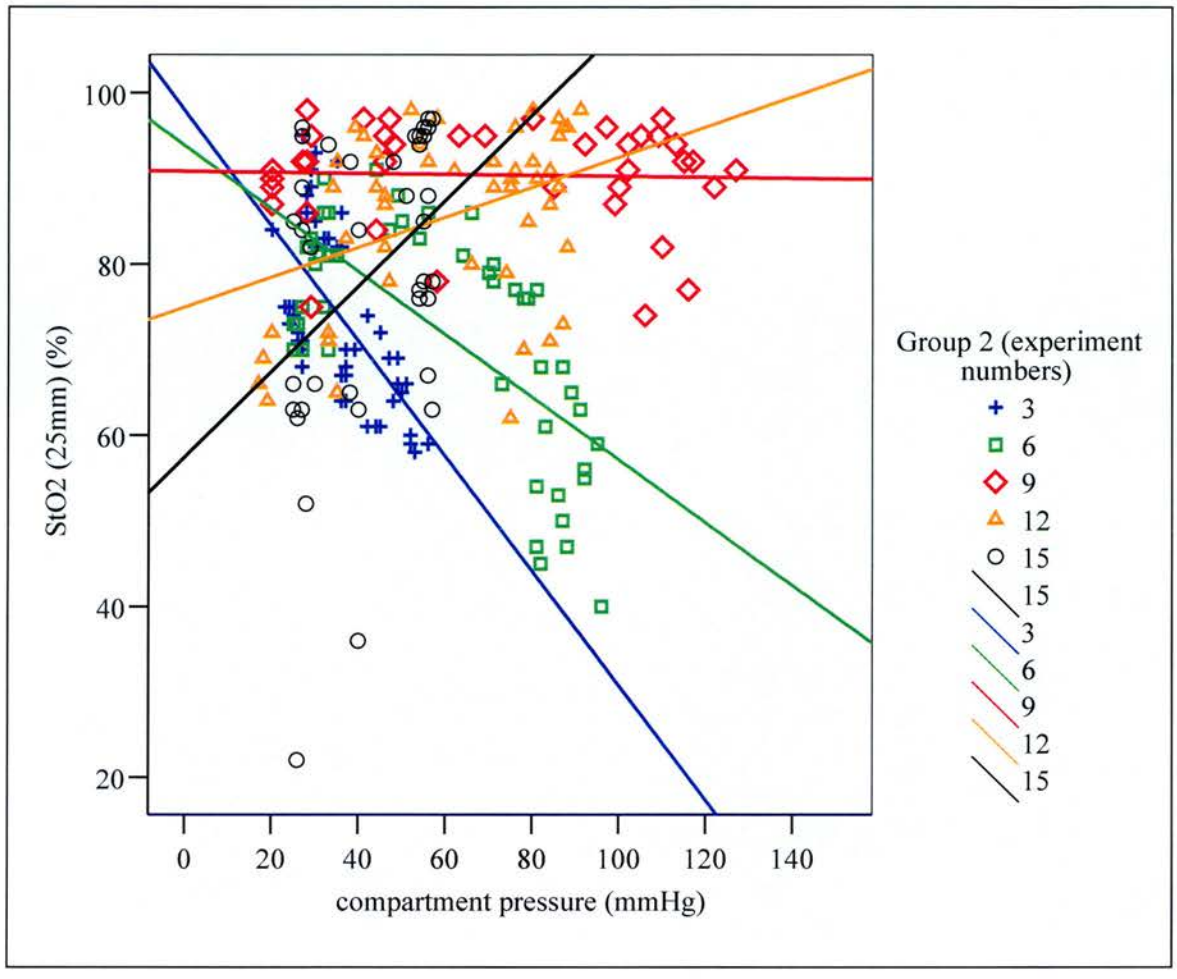

Figure 45b Scatter plots of compartment pressure (mmHg) by StO_2 (25mm) (%) for animals in group 2 (sub-cutaneous haematoma). Correlation coefficients (Spearman rho) vary from -0.7 and -0.6 ($p < 0.01$) for experiments 3 and 6 to 0.3 ($p < 0.05$) for experiments 12 and 15. Mean correlation coefficient for linear models for group 2 = 0.126, ($p = 0.06$). Using the mean value here may misrepresent the group due to the wide variety of the relationship between compartment pressure and StO_2 in the presence of a subcutaneous haematoma.

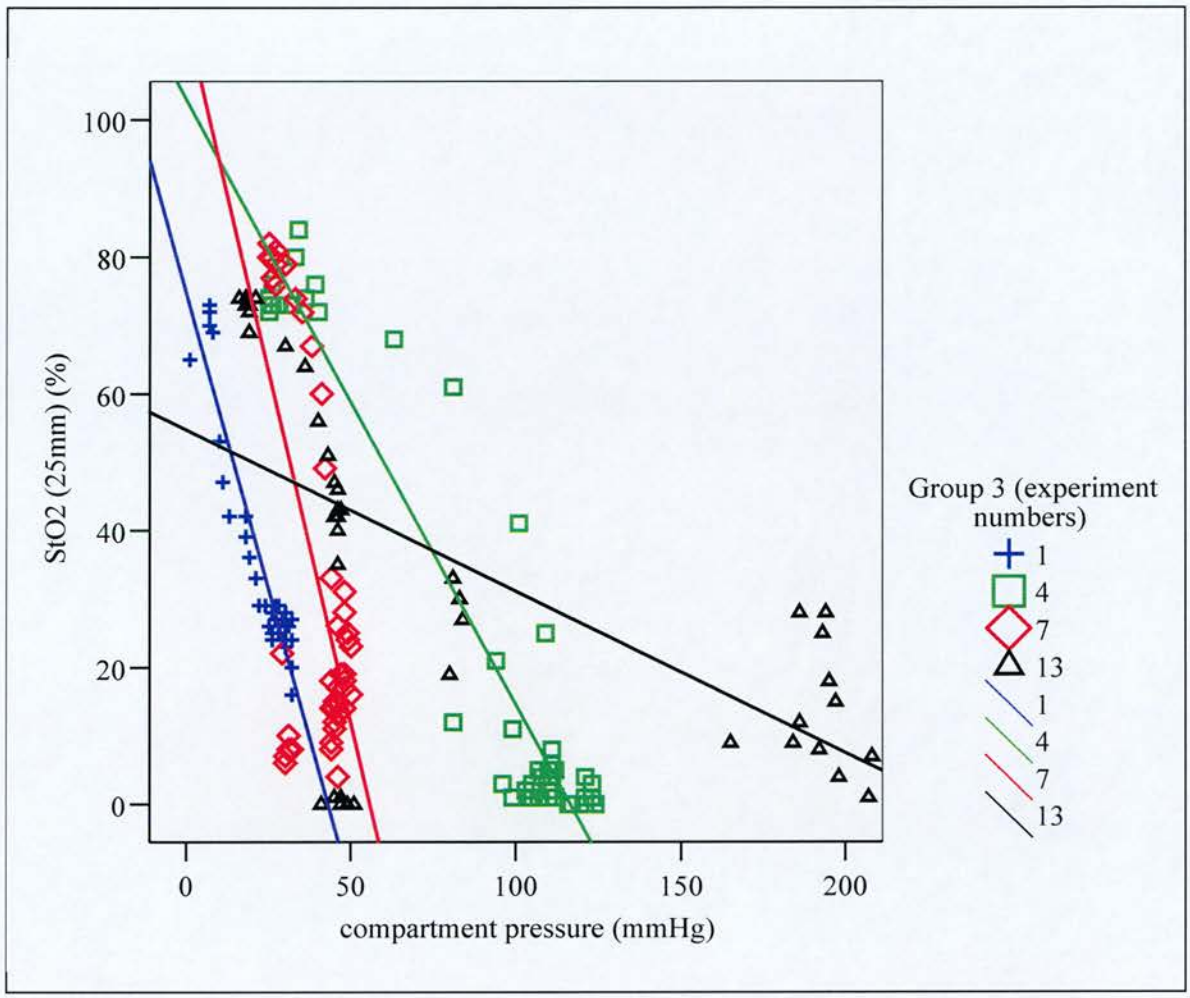

Figure 46 Scatter plots of compartment pressure (mmHg) by StO_2 (25mm) (%) for animals in group 3. Mean correlation coefficient for linear models for group 3 = –0.7. Correlations in all animals in Group 3 were significant ($p < 0.05$). Animal 10 has been excluded from group 3 in this analysis due to the presence of a subcutaneous haematoma.

The linear models representing the relationship between StO_2 and compartment pressure was significant for both the plasma infusion only (group 1) and intramuscular haematoma group (group 3) where the mean correlation was – 0.7, ($p < 0.01$). The slope of the line for animal 13 (figure 46) may have been influenced by a group of persistently low StO_2 values following the fasciotomy. This may have occurred due to severe tissue hypoxia as a result of the extremely high pressures that occurred in this animal. The same plot was

carried out for StO_2 (25mm) and compartment pressure for animals in group 2 (Figure 45b). A similar significantly negative correlation between the StO_2 and compartment pressure to that in groups 1 and 3 was seen in two animals (3 and 6), but the presence of a subcutaneous haematoma in the other three experiments caused the relationship to be lost or even reversed. The variability in this group may be due to uneven spread of the haematoma within the subcutaneous tissues. The mean correlation between StO_2 and compartment pressure was not significant in group 2 (sub-cutaneous and plasma infusion), but this must be interpreted with caution due to the variability between animals. The addition of a subcutaneous haematoma causes the expected relationship between StO_2 and compartment pressure to become unpredictable.

The fasciotomies were carried out on both sides after 30 minutes following the loss of twitch from the anterior compartment muscles. The fasciotomies were made laterally over the entire length of the anterior compartment only. The incision was positioned to allow decompression of the compartment without disturbance to the pressure monitoring catheter or the invasive pH, pCO_2 and pO_2 monitor. The remaining compartments were not decompressed.

In keeping with assessment of muscle viability following fasciotomies in human subjects, the assessment of the muscle condition in the animal model was subjective. Pale muscle was seen in the anterior compartments of animals from groups 1 and 2 in the compartment syndrome leg and those from the intramuscular group (group 3) had muscle that was more haemorrhagic. This was consistent with the red cell content of the infusions for each group (Figures 47 – 49). The interpretation of muscle twitch in response to mechanical stimulation was felt to be too subjective and 'un-blinded' to provide useful data for analysis.

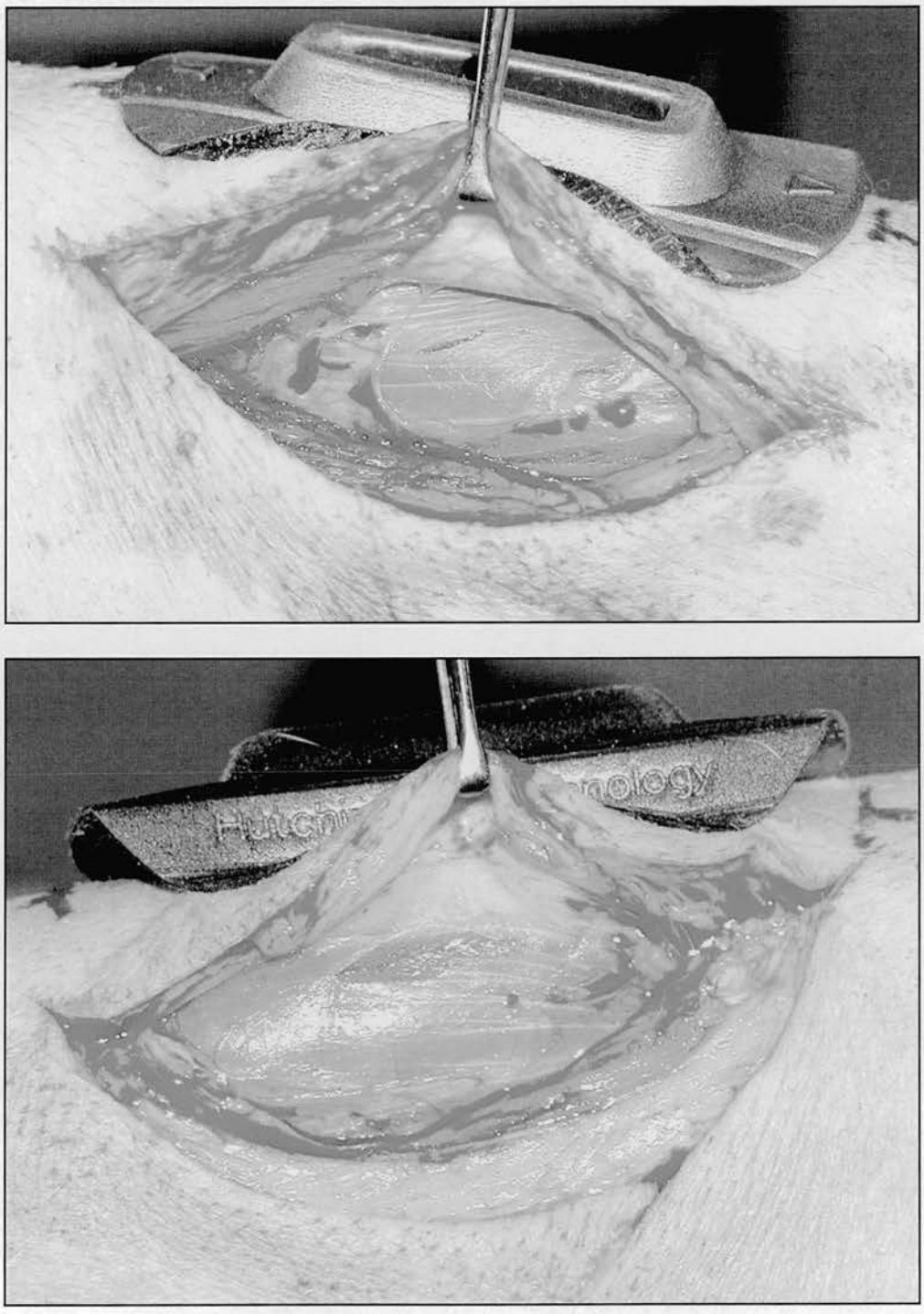

Figure 47 Anterior muscle compartments immediately following fasciotomies for a group 1 animal (plasma infusion only). Compartment syndrome (right leg) above, control limb (left leg) below. No obvious differences in the muscle colour were seen.

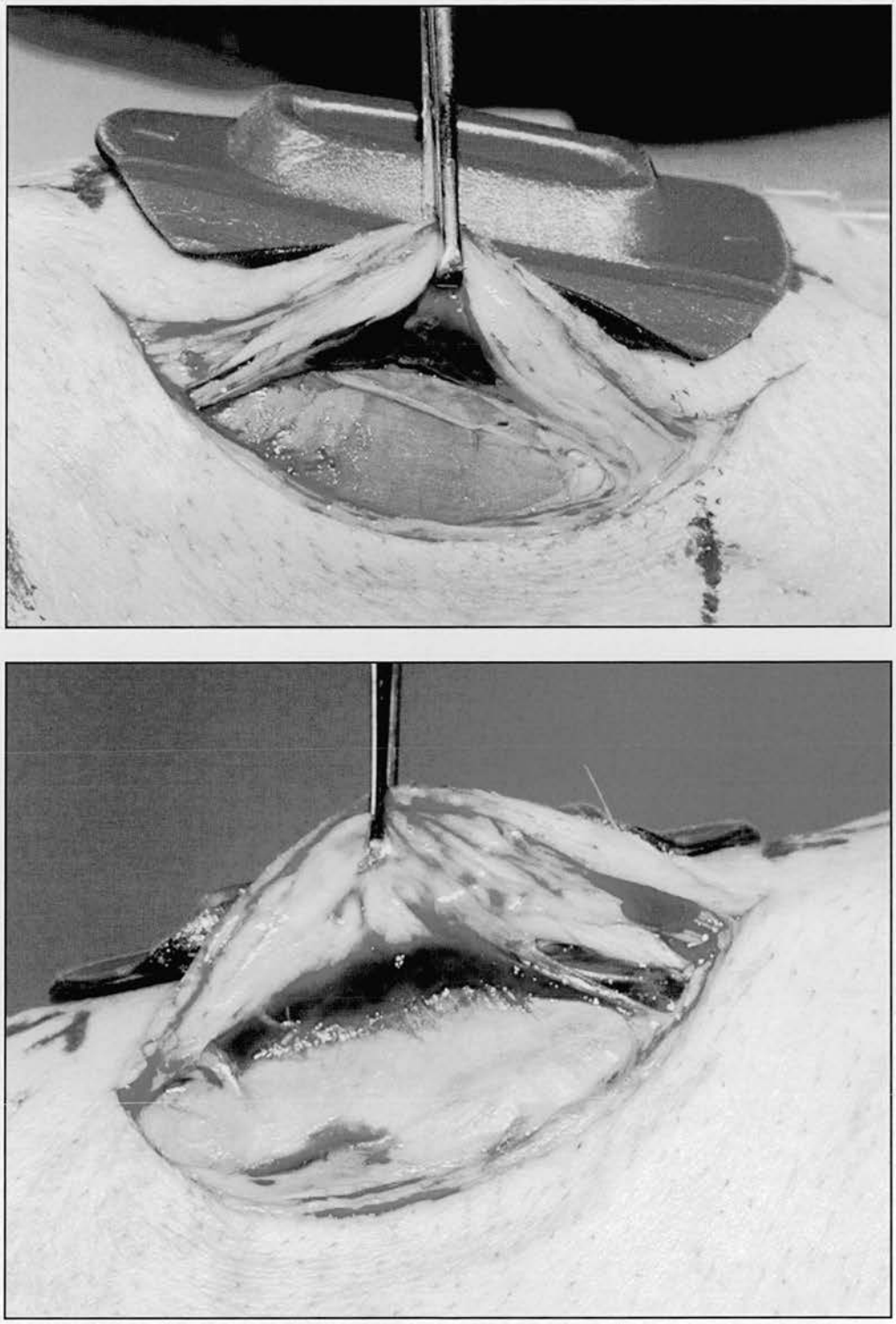

Figure 48 Anterior muscle compartments immediately following fasciotomies for a group 2 animal (sub-cutaneous haematoma and intra-muscular infusion of plasma). Compartment syndrome (right leg) above, control limb (left leg) below. Subcutaneous haematoma clearly seen in both sides.

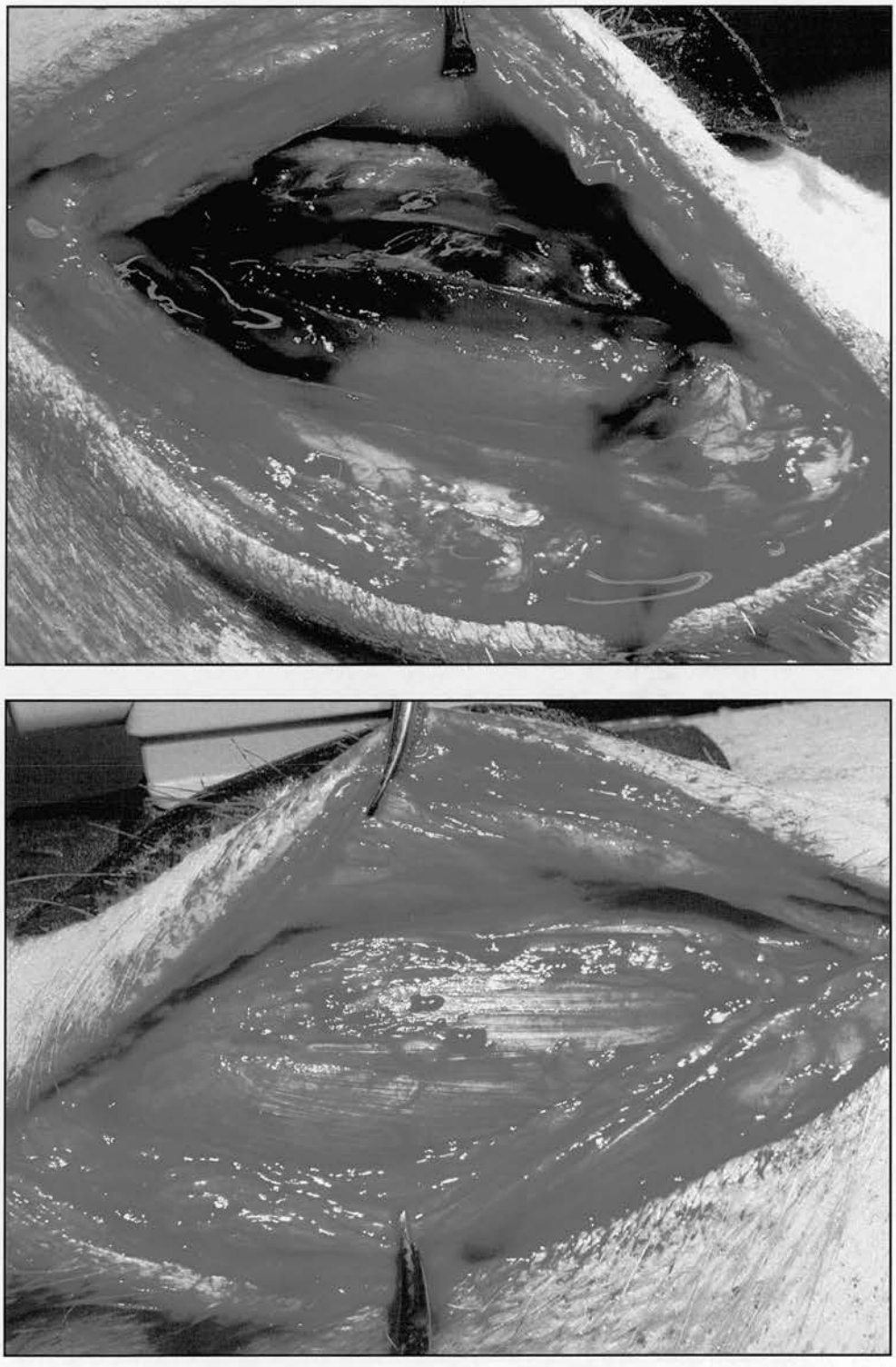

Figure 49 Anterior muscle compartments immediately following fasciotomies for a group 3 animal (intra-muscular infusion of blood). Compartment syndrome (right leg) above, control limb (left leg) below. Muscle in the compartment syndrome leg appeared haemorrhagic and swollen.

Invasive pH, pCO_2 and pO_2 monitoring.

The invasive pH, pCO_2 and pO_2 catheter (Paratrend ^{TM}) was inserted at the beginning of the experiment so that the catheter tip lay in the centre of the anterior muscle compartment on the compartment syndrome leg of each animal. The position was confirmed using ultrasound. Prior to insertion, the catheter had been calibrated within the monitor stack using standard solutions of known gas concentration (supplied by the manufacturer, Diametrics Medical Ltd, High Wycombe, UK). The monitor remained in place during and after the fasciotomy to monitor post-fasciotomy changes. The mean values have been plotted against time for the first 150 minutes of each experimental group and then separately from the point of loss of twitch (Figures 50 – 51). The fasciotomies were carried out at 30 minutes from the loss of twitch. The time course has been split to allow comparison between groups as each individual animal had a different period of time to loss of twitch.

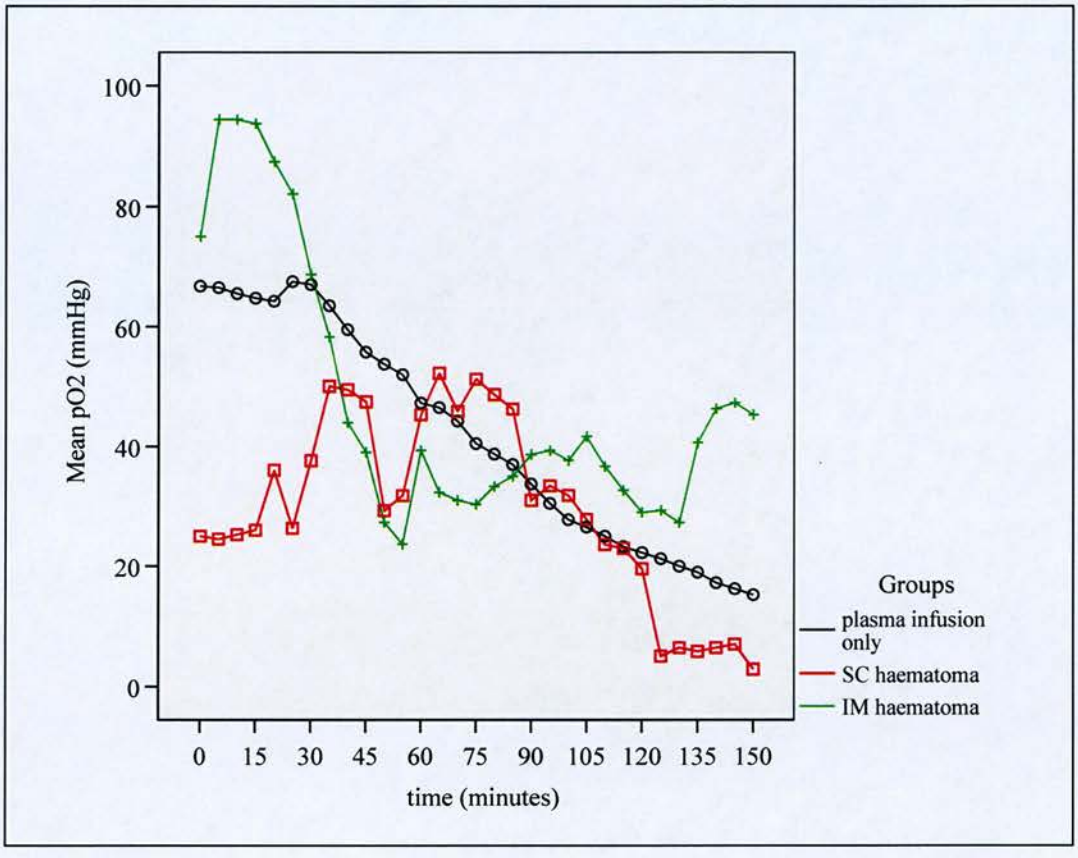

Figure 50a Mean pO_2 (mmHg) from invasive monitor in the anterior compartment muscle for each group over the first 150 minutes of each experiment.

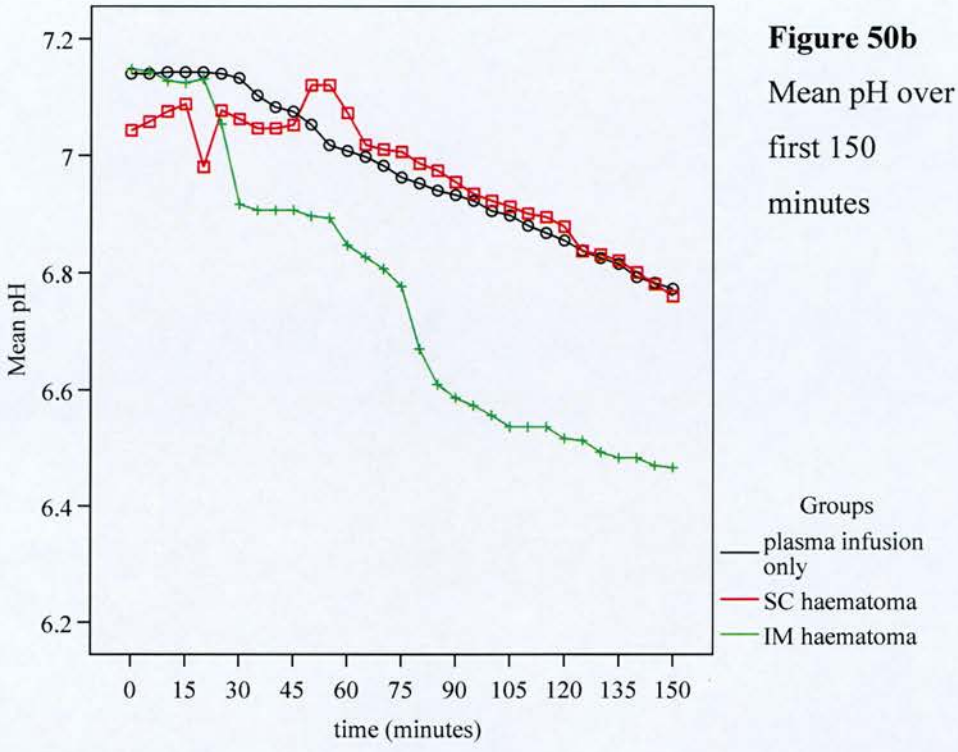

Figure 50b
Mean pH over first 150 minutes

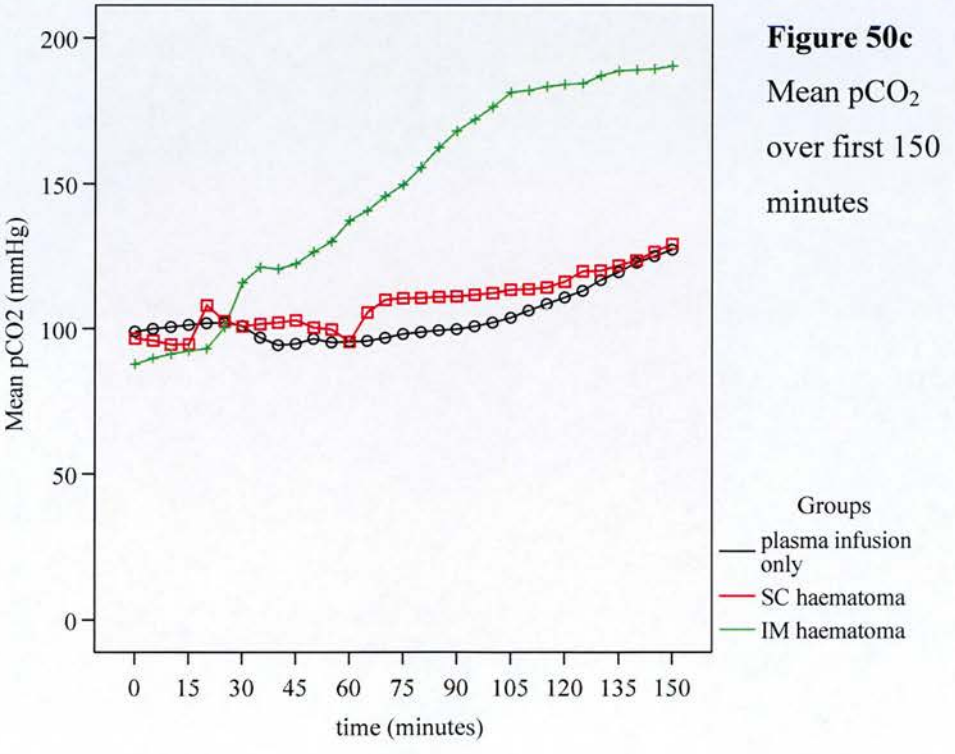

Figure 50c
Mean pCO_2 over first 150 minutes

Figure 50b, 50c Mean pH and pCO_2 (mmHg) from invasive monitor in the anterior compartment muscle for each group over the first 150 minutes of each experiment.

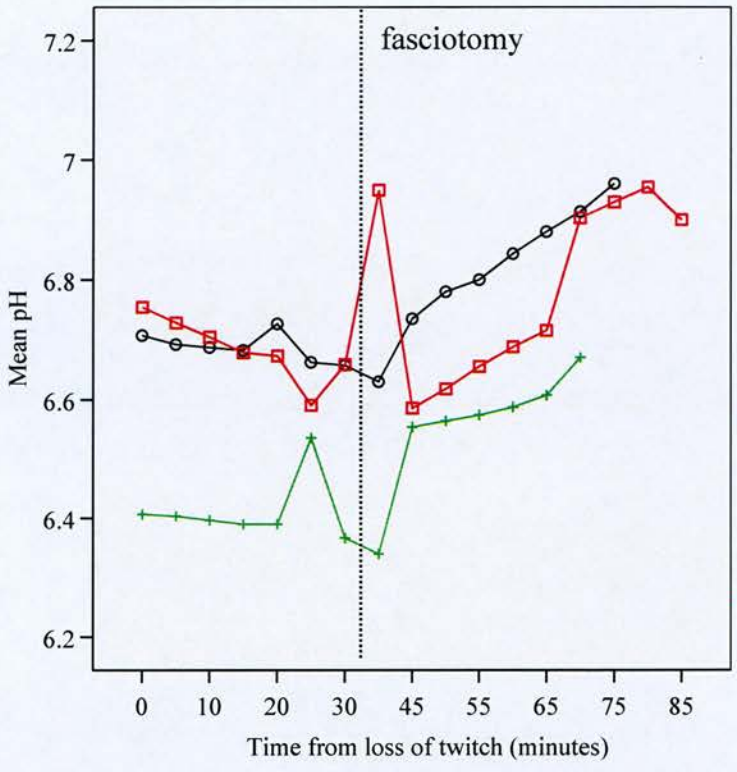

Figure 51a Mean pH following loss of twitch

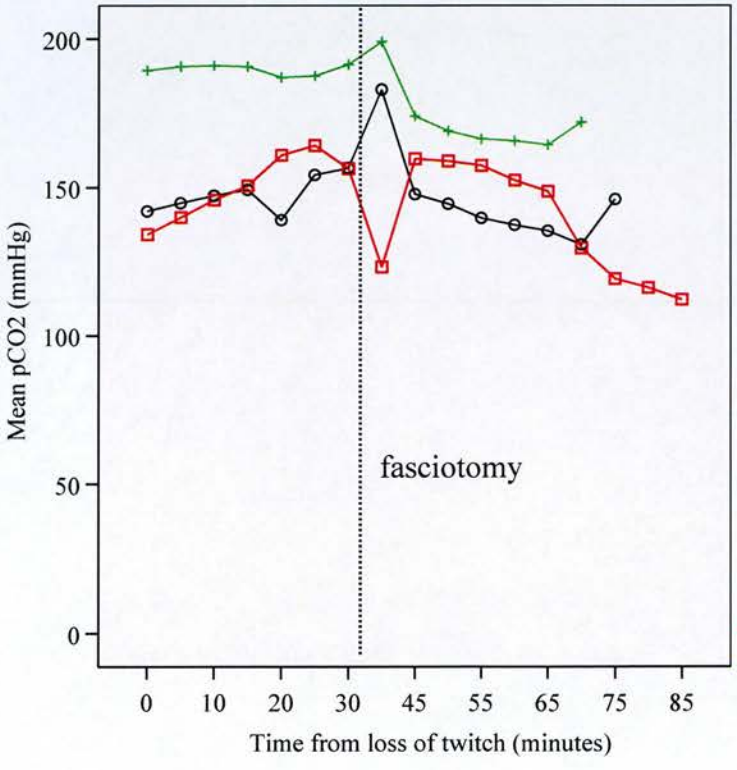

Figure 51b Mean pCO_2 following loss of twitch

Figure 51a, 51b Mean pH and pCO_2 (mmHg) from invasive monitor in the anterior compartment muscle for each group from the point of loss of twitch. Fasciotomy carried out at 30 minutes from loss of twitch.

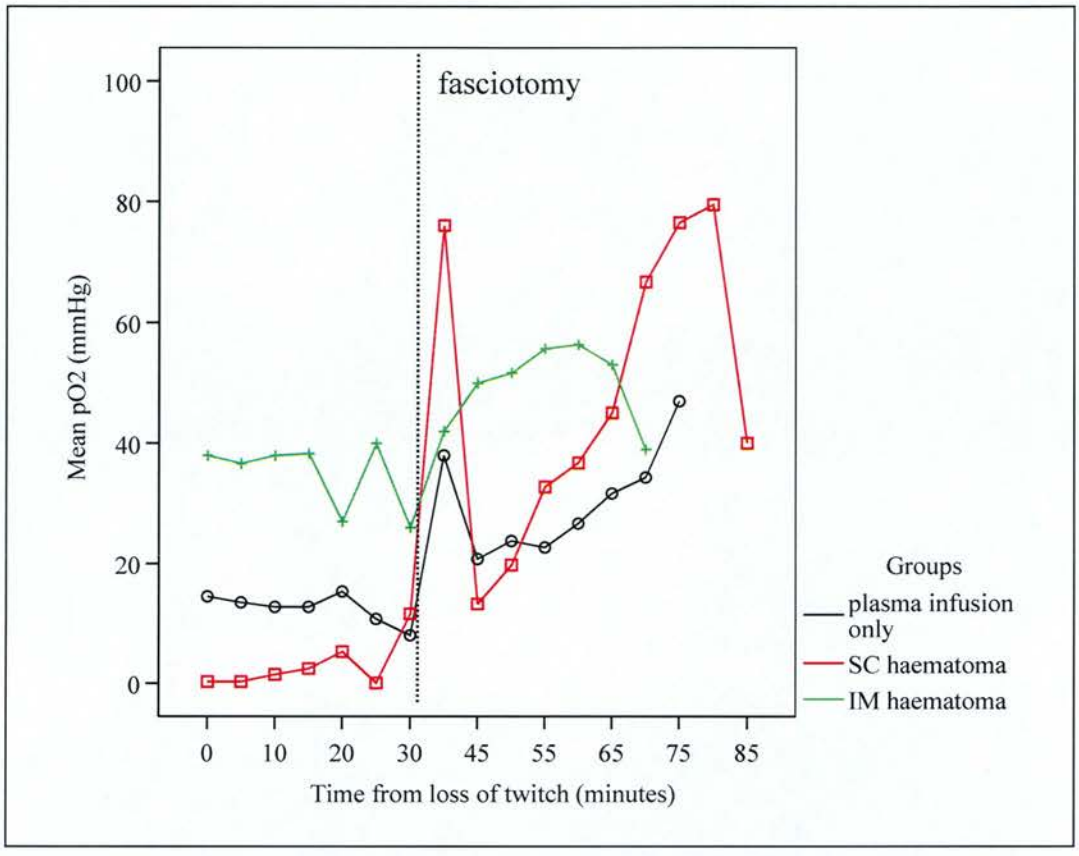

Figure 51c Mean pO_2 (mmHg) from invasive monitor in the anterior compartment muscle for each group from the loss of twitch. Fasciotomy carried out at 30 minutes

During the first fifteen minutes, before the infusions were started, there was no statistically significant difference between pO_2, pH and pCO_2 measured by the invasive catheter. During the first 150 minutes, Figure 47 reveals a fall in pO_2 and pH and a rise in pCO_2 in all three groups. The changes in pO_2, pH and pCO_2 were all highly significant over the pre-fasciotomy period (Table 28). The tracing for the pO_2 was more variable between animals but it was observed that the fall in pO_2 was more rapid than the decline in pH or rise in pCO_2. A copy of the output for animal 8 illustrates this over the development of the acute compartment syndrome and subsequent fasciotomy (Figure 52). The intra-muscular temperature was recorded, alongside the core temperature (rectal) of each animal. The mean temperatures fell in all groups (Figure 53). The intramuscular

temperature was found to be lower than the core temperature in all groups. The intramuscular temperature fall was not significant in group 3 ($p = 0.3$) and the core temperature change was not significant in group 1 ($p = 0.07$).

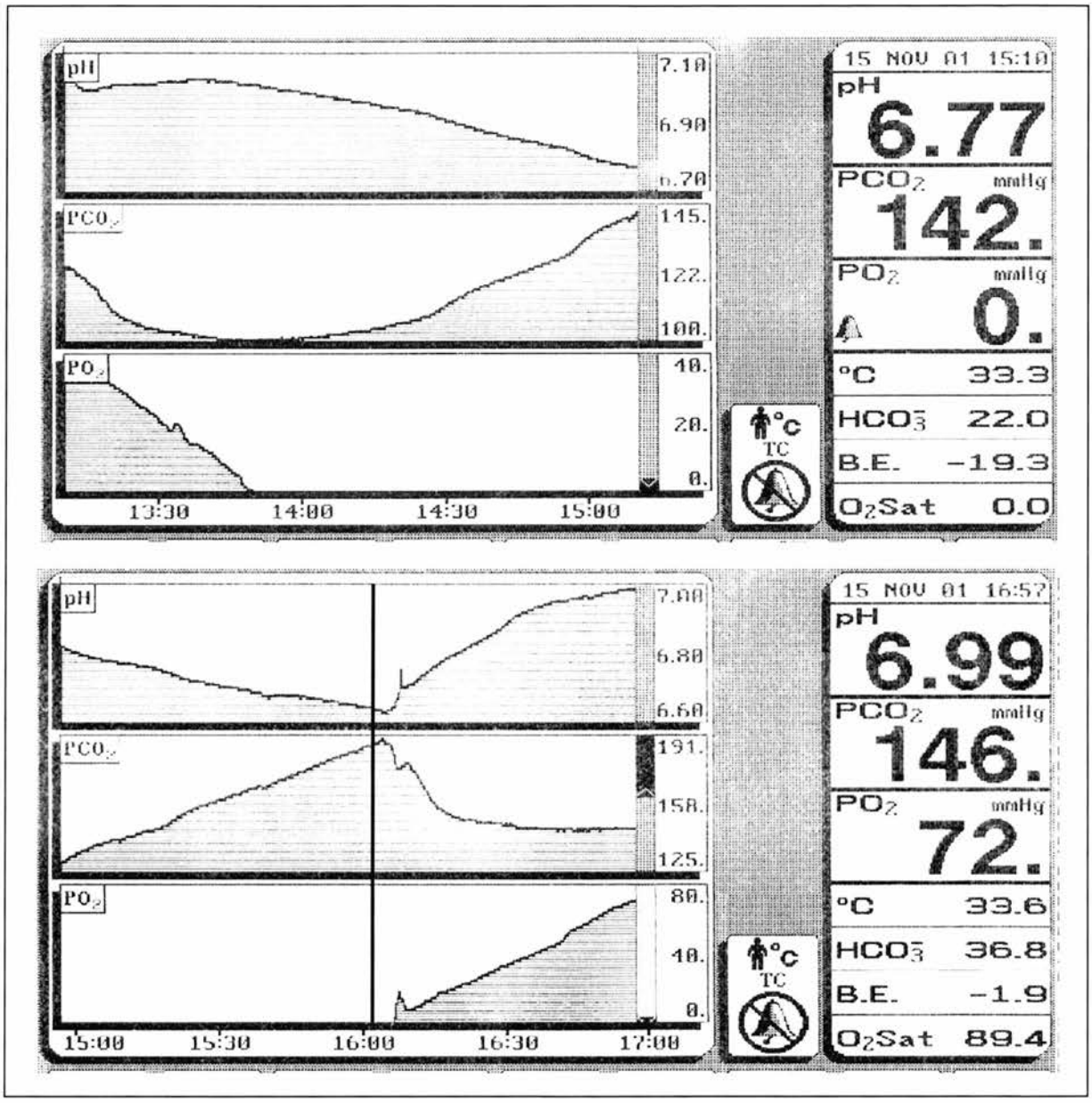

Figure 52 Intramuscular pH, pCO_2 (mmHg), pO_2 (mmHg) output for animal 8 (plasma infusion only – group1). The two printouts are consecutive, with time on the x-axis. Values in the right hand box correspond to the time point at the right side of the graph. The rapid fall in pO_2 is demonstrated, followed by later changes in pH and pCO_2. The black vertical line represents the fasciotomy, the pH and pO_2 reverse, whereas the pCO_2 only partially normalizes in the time observed here. pO_2 tracings were found to be variable between animals and therefore the use of mean values, as in earlier figures, can hide the relative changes between metabolites that were observed over time.

	Group 1. Plasma infusion alone			Group 2. SC haematoma and plasma infusion			Group 3[a] Intramuscular infusion of blood		
	Initial	Pre-fasciotomy	Significance	Initial	Pre-fasciotomy	Significance	Initial	Pre-fasciotomy	Significance
pH	7.14	6.68	$p < 0.01$	7.06	6.68	$p < 0.01$	7.13	6.4	$p < 0.01$
pCO_2 (mmHg)	100	147	$p < 0.01$	95	149	$p < 0.01$	90	189	$p < 0.01$
pO_2 (mmHg)	66	12	$p < 0.01$	25	3	$p < 0.01$	89	35	$p < 0.01$
IM temp (^oC)	33.6	32.7	$p < 0.01$	34.5	33.5	$p < 0.01$	32.2	31.3	$p = 0.3$
Compartment pressure (mmHg)	28	107	$p < 0.01$	23	78	$p < 0.01$	19	96	$p < 0.01$
StO_2 (25mm) (%)	74	12	$p < 0.01$	72	76	$p = 0.3$	74	12	$p < 0.01$

Table 28 Mean values for pH, pCO_2, pO_2, intra-muscular temperature, compartment pressure and StO_2 (25mm) during the initial 15 minutes, prior to start of infusions and for the 30 minutes following the loss of twitch (immediately pre-fasciotomy). Intra-muscular temperature fell for all animals, but was not significant for animals in group 3. The slight rise in StO_2 (25mm) in the presence of a subcutaneous haematoma (group 2) is in contrast to the highly significant changes recorded by the invasive catheter in the same animals. [a] Animal 10 excluded.

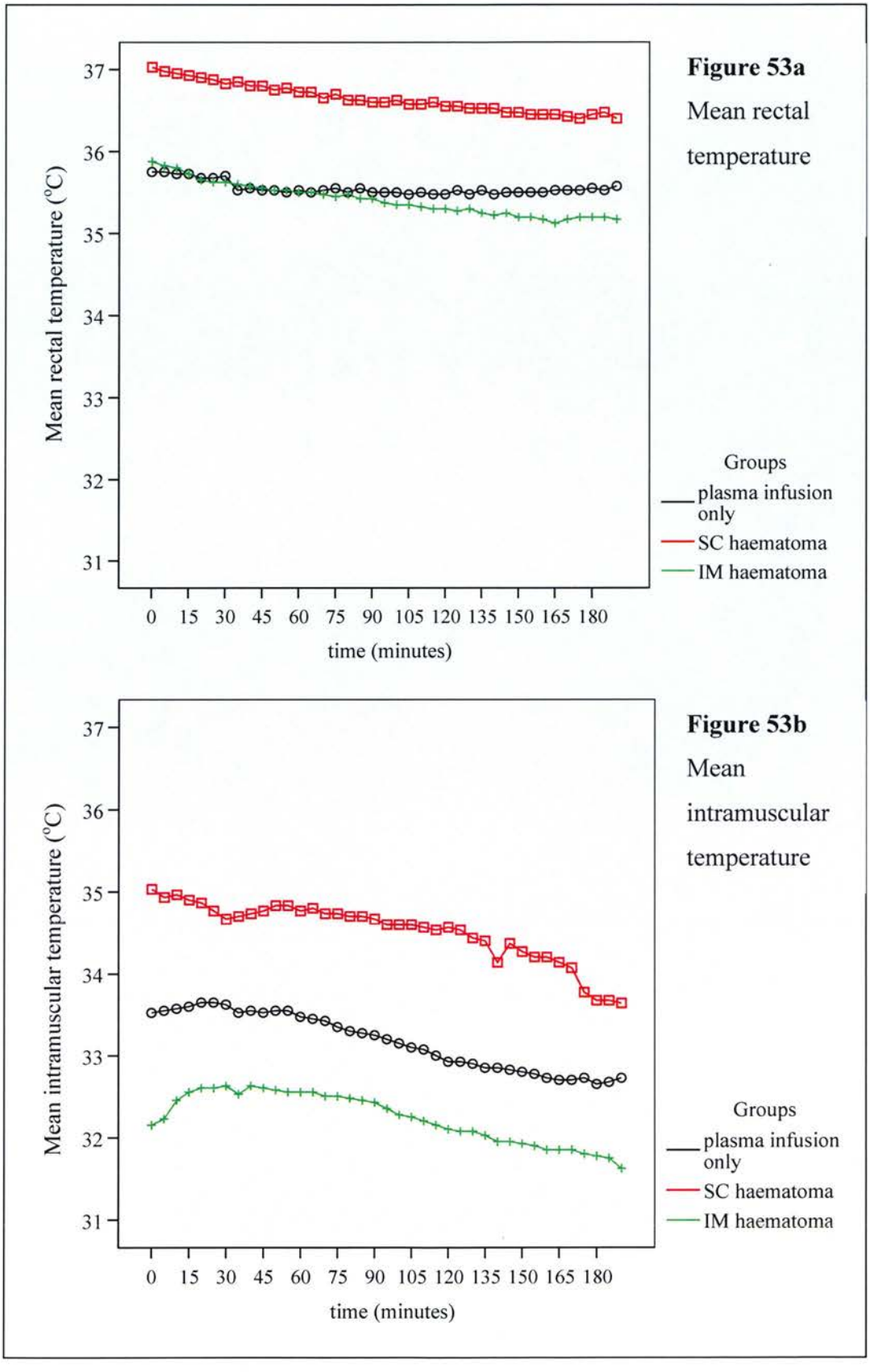

Figure 53a Mean rectal temperature

Figure 53b Mean intramuscular temperature

Figure 53 Mean rectal and intramuscular temperatures from the anterior compartments of the compartment syndrome legs over the initial 190 min period (°C).

In group 1 (plasma infusion only), two animals were found to have a rising temperature in contrast to all other experimental animals and therefore the mean values for the group appears relatively horizontal. It is known that *Landrace* pigs can carry the gene responsible for susceptibility for malignant hyperpyrexia in response to halothane anaesthesia (Brodbelt and Taylor, 1998). This is a possible cause of rising temperature during anaesthesia in the absence of any warming devices. At the beginning of the procedure, before any infusions had started, the core (rectal) temperature of animals in the subcutaneous haematoma group had a significantly higher temperature (mean 36.9 ^{o}C, $p < 0.01$). A significant difference in intramuscular temperature was also found between all groups at the beginning of the experiments ($p<0.01$). This significant difference continued throughout the whole of the pre-fasciotomy period (Figure 53b).

The pH, pCO_2 and pO_2 monitoring has allowed changes in the intramuscular environment to be determined over the duration of the experiment. In order to demonstrate that the values recorded were not simply a result of changes that had occurred in the infusion, which were then picked up by the pH, pCO_2 and pO_2 catheter, the invasive monitor was placed in the infusion syringe at the end of each procedure and the pH, pCO_2, pO_2 and temperature were recorded. Table 29 compares the mean intramuscular pH, pCO_2 and pO_2 at the start of the experiments and at the loss of twitch, indicating the development of an acute compartment syndrome, with the mean pH, pCO_2 and pO_2 of each infusion inside the syringe at the end of the experiments.

	Mean pH (± SD)			**Mean pCO_2** (mmHg) (± SD)			**pO_2** (mmHg) (± SD)			**Temperature** (^oC) (± SD)		
	Start	ACS	Infusion	Start	ACS	Infusion	Start	ACS	Infusion	Start	ACS	Infusion
Group 1 Plasma infusion alone	**7.14** (± 0.05)	**6.71** (± 0.14)	**7.11** (± 0.24)	**99.0** (± 14.4)	**140.7** (± 25.7)	**58.0** (± 25.7)	**66.7** (± 22.2)	**13.5** (± 18.9)	**114.5** (± 11.0)	**33.5** (± 0.5)	**32.7** (± 0.7)	**25.8** (± 1.5)
Group 2 Subcutaneous haematoma	**6.97** (± 0.15)	**6.76** (± 0.21)	**6.96** (± 0.29)	**96.9** (± 19.4)	**126.9** (± 41.8)	**78.9** (± 33.3)	**26.7** (± 34.9)	**2.0** (± 3.3)	**107.5** (± 28.2)	**34.5** (± 1.2)	**33.6** (± 1.8)	**26.1** (± 0.9)
Group3 Intramuscular haematoma	**7.15** (± 0.08)	**6.41** (± 0.28)	**6.62** (± 0.29)	**87.6** (± 14.2)	**189.3** (± 13.4)	**133.7** (± 27.3)	**75.0** (± 55.6)	**38.0** (± 32.9)	**84.7** (± 16.6)	**32.0** (± 2.2)	**31.7** (± 2.8)	**24.9** (± 2.9)

Table 29 Mean pH, pCO_2 (mmHg), pO_2 (mmHg) and temperature (^oC) values at the start, at the loss of muscle twitch (ACS – acute compartment syndrome) and values taken from the infusion syringe at the end of each procedure (Infusions = plasma for group 1 and 2, whole blood for group 3).

The mean pH of the infusion in the syringe at the end of the experiments for all groups was greater than the intramuscular pH at the time of development of an acute compartment syndrome. Similarly, the mean pCO_2 in the infusion was lower than the mean pCO_2 generated at the point of loss of muscle twitch. The mean pO_2 in the infusion syringes of the three groups ranged from 84.7 mmHg to 114.5 mmHg. This compares to the intramuscular mean values of pO_2, which ranged from 38.0 mmHg to 13.5 mmHg ($p < 0.01$ for all groups). These results indicate that the intramuscular chemical changes that were measured by the invasive catheter were not a result of the catheter recording the pH, pCO_2 and pO_2 values of infusion fluid that could have tracked across to the monitoring catheter from the infusion catheter.

The infusion fluid (Table 29) was found to be significantly cooler than the intramuscular temperature ($p < 0.01$ for all groups). This is likely to have contributed to the reduction in the intramuscular temperature that was observed over the experimental period.

The intramuscular mean pO_2 for animals with a sub-cutaneous haematoma was found to be lower at the start and at the development of an acute compartment syndrome than animals in other groups. This difference, however, was not significant when compared to group 1 animals ($p = 0.17$ at the start, $p = 0.2$ at the development of ACS). Animals from group 2 were known to have a significantly lower systemic pO_2 measured by arterial blood gases at the start and at the development of an ACS (Figure 33). The only significant difference between the groups that was detected on measurement of the intramuscular parameters was of a high mean pCO_2 at the development of an ACS in animals from group 3, intramuscular haematoma, when compared to animals in group 1, plasma infusion only ($p = 0.04$).

Ultrasound measurements

Measurements using a portable ultrasound scanner were carried out immediately following the initial set-up on each leg and immediately prior to the fasciotomy at the same site. For animals in group 2, measurements were also made following the injection of 25mls into the sub-cutaneous tissue overlying the anterior compartment. The skin had been marked so that the scanner could be accurately repositioned for the second measurement. Two measurements over the midpoint of each anterior compartment were made; firstly, the distance between the skin and the deep fascia – the sub-cutaneous (SC) depth and secondly, the distance between the anterior and posterior border of the *Peroneus Tertius* and *Extensor Digitorum Longus* muscle belly – the anterior compartment (AC) depth (Figures 20, 30).

There were mechanical problems with the ultrasound scanner during experiments 5 and 6 and so measurements were complete for only four animals in groups 1 and 2.

The mass of the animals varied between the experiments as the animals were originally acquired in two batches and so during the course of the investigation period the animals had continued to gain weight. To avoid potential errors due to differences in mass or body composition the experiments were carried out sequentially: group 1, group 2 then group 3 before starting another group 1 experiment, *etc*. Animals were not pre-selected into any particular group. Figure 54 demonstrates the initial measurements of subcutaneous and anterior compartment depths compared to animal mass. The graph shows the presence of two distinct batches of animals with masses above and below 100kgs and differing compositions. Animals with a mean mass of 89 kg had a mean SC depth of 4.0 mm (SD ± 0.3 mm) and mean AC depth of 18.4 mm (SD ± 3.0 mm), whereas the batch with a mean mass 128 kg had a mean SC depth of 6.3 mm (SD ± 1.3 mm) and mean AC depth of 14.1 mm (SD ± 3.0 mm). The increase in SC thickness for the larger

animals was highly significant ($p < 0.01$), whereas the difference in AC depth was insignificant with this number of animals.

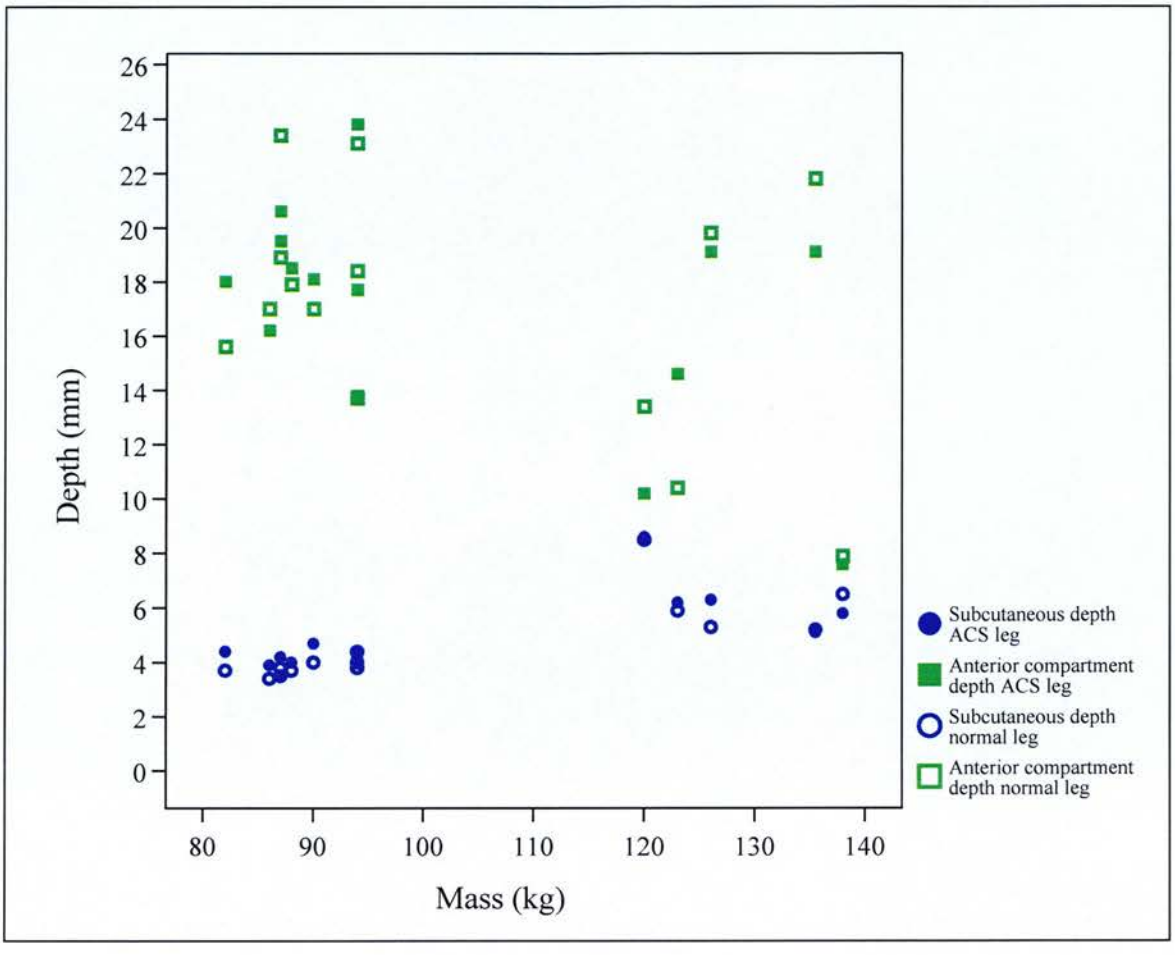

Figure 54 Pre-experimental measurements of animal mass plotted against subcutaneous depth (mm) and anterior compartment depth (mm) for acute compartment syndrome legs and normal legs.

In view of the differences identified above the importance of splitting the batches of animals into the different groups is clear. Table 30 confirms that the groups had similar mean values and no statistically significant differences between measurements at any single time point were found.

			Group 1. Plasma infusion alone **Mean value (mm) (± SD)**	**Group 2.** SC haematoma and plasma infusion **Mean value (mm) (± SD)**	**Group 3** Intramuscular infusion of blood [a]. **Mean value (mm) (± SD)**
compartment syndrome leg	Initial measurement	Subcutaneous depth	**4.8** (± 0.9)	**4.5** (± 1.0)	**5.7** (± 2.2)
		Anterior compartment depth	**17.8** (± 4.0)	**16.4** (± 6.0)	**16.0** (± 4.0)
	Pre-fasciotomy	Subcutaneous depth	**4.2** (± 0.4)	**5.7** (± 1.6)	**4.7** (± 0.7)
		Anterior compartment depth	**18.9** (± 4.6)	**18.6** (± 7.6)	**16.7** (± 3.7)
normal leg	Initial measurement	Subcutaneous depth	**4.6** (± 0.9)	**4.3** (± 1.4)	**5.2** (± 2.3)
		Anterior compartment depth	**17.4** (± 5.4)	**16.4** (± 6.5)	**17.0** (± 2.7)
	Pre-fasciotomy	Subcutaneous depth	**4.2** (± 0.9)	**6.9** (± 3.6)	**3.6** (± 0.8)
		Anterior compartment depth	**16.4** (± 3.8)	**18.3** (± 5.0)	**13.3** (± 4.3)

Table 30 Mean distances (mm) (± SD) between skin surface and deep fascia (Subcutaneous depth), and distance across tibialis anterior muscle (anterior compartment depth) taken immediately before the infusions were started and immediately before fasciotomies were carried out. No statistical significant difference between animals in any group.

Animals that received a subcutaneous haematoma (group 2) showed an initial increase in SC depth from a mean 4.5 mm (SD ± 1.0 mm) to 10.4 mm (SD ± 3.8 mm) ($p < 0.05$). After the period of infusion and once the acute compartment syndrome had been established, the SC depth in the group 2 animals had fallen to a mean of 5.7 mm (SD ± 3.8 mm). This was not significantly different from the pre-fasciotomy values for SC depth in groups 1 and 3 where the mean SC depth was 4.2 mm (SD ± 0.4 mm) and 4.7 mm (SD ± 0.7 mm) respectively ($p = 0.14$ and $p = 0.4$). Over the course of the experiment no group demonstrated a significant change in the subcutaneous depth that could potentially contribute to the change in StO_2 values that were measured.

Similarly, when the initial measurements of the AC depth were compared to those taken prior to the fasciotomy, no significant changes in the anterior compartment depth were detected either between groups or over the duration of the experiment.

Skin and adipose layer contribution to StO_2 values.

The skin and adipose layer contribution was examined in four animals at the end of the main investigation. The tissues were studied in the following combinations.

1. Normal subcutaneous tissue and muscle
2. Ischaemic subcutaneous tissue and normal muscle
3. Normal muscle alone
4. Ischaemic muscle alone
5. Ischaemic subcutaneous tissue and ischaemic muscle

No significant differences were found in the value of StO_2 obtained over depths of 25 and 12 mm when normal tissue, ischaemic skin and normal muscle and normal muscle alone were examined (Table 31). The mean skin and adipose thickness was 3.7 mm (range 3.3 – 4.8 mm). The creation of the ischaemic patch of skin and adipose tissue caused a mean 3% fall in StO_2 for both the 25 mm and 12 mm NIRS interfaces. This was not a significant fall in StO_2 with only four animals ($p = 0.2$ and $p = 0.3$).

Removal of the skin and adipose layer from the muscle surface allowed the interface to be placed directly onto normal perfused muscle. The mean StO_2 increased, for both 12 mm and 25 mm by approximately 10% above the normal skin and muscle and 15% above the ischaemic skin and perfused muscle combination. Although the low standard deviations, particularly at 25 mm over perfused muscle, indicate a low level of variation between animals, these differences were not significant. This result suggests that a 3.7 mm thickness of skin and adipose tissue, irrespective of skin ischaemia, could reduce the StO_2 value by 10% compared to the StO_2 value had it been obtained directly from the perfused muscle below.

Measurement of the StO_2 directly on muscle that had been underperfused for 15 minutes by the occlusion of the common femoral artery demonstrated a significant fall in StO_2 at both 25 mm and 12 mm ($p = 0.04$ and $p = 0.02$). The re-introduction of the ischaemic skin and adipose tissue over the underperfused muscle, surprisingly, did not cause any further significant changes to the StO_2 value over 25 mm or 12 mm. This was in contrast to when the skin and adipose was removed and measurements were made directly from the muscle. The only significant difference that was identified between the 25 mm and 12 mm NIRS interfaces occurred when recordings were made over both the ischaemic skin and adipose tissue lying on the underperfused muscle (Table 31).

	Number of animals	**Mean StO2 (%) over 25mm (± SD)**	**Mean StO2 (%) over 12mm (± SD)**	**Significance**
Normal subcutaneous tissue and muscle	n = 4	**82** (± 3.6)	**82** (± 4.2)	p = 1.0
Ischaemic subcutaneous tissue and normal muscle	n = 4	**79** (± 7.5)	**79** (± 7.6)	p = 1.0
Normal muscle alone	n = 4	**95** (± 0.6)	**93** (± 5.0)	p = 0.5
Ischaemic muscle alone	n = 4	**46** (± 16.1)	**60** (± 12.0)	p = 0.2
Ischaemic subcutaneous tissue and ischaemic muscle	n = 4	**46** (± 11.8)	**68** (± 4.1)	p = 0.02*

Table 31 Mean StO_2 (%) over 25 and 12 mm for combinations of skin and muscle, ischaemic and normal. * A statistically significant difference was observed between the 25 mm and 12 mm values for ischaemic skin and muscle together.

3.4 Discussion of Animal Study

The animal study has reproduced the porcine model of a developing acute compartment syndrome and has reproduced the finding of an inverse relationship between the measurement of StO_2 by near-infrared spectroscopy and compartment pressure (Garr *et al.*,1999). This study has demonstrated, however, that in the presence of a subcutaneous haematoma in the light pathway, StO_2 does not correlate with compartment pressure. The development of an acute compartment syndrome due to an expanding intramuscular haematoma does not effect the correlation between StO_2 and compartment pressure.

It was possible to complete this study with 15 animals only, as an interim analysis suggested a clear significant difference in StO_2 between the experimental groups. It could not be justified to carry out further experiments in order to reach statistical significance in some areas of the study as it was felt that a strong conclusion could be reached with regard to the effect of a sub-cutaneous haematoma on the NIRS measurements. The additional study that looked at the effect made by the skin and adipose tissue on the NIRS signal, demonstrated a possible reduction of approximately10% in the StO_2 value when the near-infrared signal travelled through skin and adipose tissue, whether normal or ischaemic. This difference was not statistically significant with the numbers used. It was felt that this relationship could be further investigated in the future using sterilised intra-operative NIRS equipment and therefore the additional animals that had been included in the proposal were not ordered.

Measurement of initial and pre-fasciotomy arterial blood gases allowed a comparison between the three groups of animals. The finding of a significantly low initial mean pO_2 in animals with a subcutaneous haematoma (group 2) was

unexpected. A low, but not significant, intramuscular mean pO_2 was also detected in this group. All animals had been treated identically and the cause for this observation is unclear. No particular animal appeared as an outlier with regard to pO_2 that could have skewed the mean value. The animals were not mechanically ventilated and the anaesthetic requirements for each group were not recorded. It is possible that the increased painful stimulus of a subcutaneous haematoma in this group resulted in the requirement for a small increase in anaesthetic concentration to keep the animal anaesthetised, which may have caused some hypoventilation resulting in hypoxaemia. NIRS in these animals with a subcutaneous haematoma demonstrated an increased StO_2 despite the known relative systemic hypoxaemia. Clearly this was unintentional, but in fact reinforces the main findings of the animal study. During the course of the experiment, all animals demonstrated arterial blood gas changes suggestive of increasing acidosis and haemoconcentration. The latter was likely to be due to a failure to maintain adequate hydration over the duration of the experiment. The increasing pCO_2 and HCO_3 combined with a falling pH is suggestive of an acute respiratory acidosis, the most likely cause would be secondary to hypoventilation under the anaesthetic (Flenley, 1971). The potassium levels were also found to rise during the experiments; this may have been secondary to the acidosis or as a result of tissue damage from the developing acute compartment syndrome. The experimental design did not allow for an additional animal to be used without an acute compartment syndrome in order to identify the reason for these systemic changes as each animal had the contralateral limb as an individual control.

Previous animal work with NIRS suggested that an increase in compartment pressure over 150 minutes was matched by a fall in StO_2 from 80% to 20% (Garr *et al.*,1999). The mechanism for increasing the compartment pressure in the study by

Garr *et al.* (1999), along with others previously published, was to elevate an infusion bag to create hydrostatic pressure and therefore control the compartment pressure (Sheridan and Matsen, 1975; Mubarak *et al.*, 1976; Hargens *et al.*, 1981). Many of these earlier studies investigated the late cellular effects of having raised compartment pressure over a prolonged period of time and therefore the use of an elevated infusion bag was appropriate. The animal model in this study was concerned with comparing the ability of an instrument to non-invasively detect a developing acute compartment syndrome with an invasive pressure monitor that directly recorded the pressure. This study was not concerned with maintaining a steady pressure over many hours, but to most accurately reproduce a compartment pressure that rose smoothly and steadily each time. For this reason a syringe infusion pump with a set delivery rate was chosen. A similar infusion pump has been used to investigate non-invasive compartment monitoring in a canine model (Steinberg and Gelberman, 1992).

The resting pressure and the pressure in the anterior compartments prior to the loss of twitch in this porcine model were greater than expected. Garr *et al.*, (1999), reported a mean resting pressure of 13.4 mmHg and a pressure at the loss of twitch of 43.4 mmHg (range 27 – 74 mmHg). The mean animal mass in the study by Garr *et al.* was 18 kg compared to 105 kg for this study. As the animals were larger it is likely that the extended position of the rear leg with the animal supine created a slightly elevated resting pressure in the anterior compartments in these animals compared to those in the earlier work.

The loss of muscle twitch after electrical stimulation was used as a marker of loss of function of the neuromuscular unit (Garr *et al,.* 1999; Arbabi *et al.*, 1999). The loss of neuromuscular function has been assumed to be because of the development of muscle ischaemia due to hypoperfusion. It is likely that in an animal

model run over a short time period, the development of muscle ischaemia may coincide with a mechanical volume effect that is caused by the infusion of fluid into a restricted space such as the muscle compartment, which in turn prevents the muscle from contracting as normal. In this case the muscle compartment, at a certain pressure, would fail to contract as a unit due to the mechanical effect either in isolation or in combination with the developing ischaemia. In a small compartment, such as in the 18 kg animals of the Garr *et al.* study, the mechanical effect may produce loss of twitch at a lower compartment pressure than the point of loss of twitch in the present study. For example, the force applied perpendicularly to oppose the contraction of a single muscle fibre would need to be increased considerably to oppose the contraction of multiple fibres placed in parallel. It is not proposed that the pressure in an acute compartment syndrome is dependant on the size of the compartment. In these relatively short experiments, compared to a 'clinical' acute compartment syndrome, the loss of twitch may not be wholly caused by reduced neuromuscular function, but may in part be attributed by the rapid infusion of fluid into a constrained space.

In this animal model, a value of minus 43 mmHg has been calculated for the mean ΔP value (diastolic blood pressure – compartment pressure) at the point of loss of muscle twitch. This is in contrast to the clinical study where a ΔP value of less than 30 mmHg was taken as the threshold for a fasciotomy. The porcine model has a low diastolic blood pressure, of approximately 50 mmHg, compared to man. This is combined with the high compartment pressure in the model, giving rise to low ΔP values. The experiment was not designed to confirm the accuracy of the ΔP value in the compartment and therefore any extrapolation of the ΔP values to clinical practice should be made with caution. The mean perfusion pressure (mean arterial pressure –

compartment pressure) at the point of loss of twitch calculated by Garr *et al.*, 1999, was 13.6 mmHg (SD ± 17.3). The corresponding mean value for this study was –11.6 mmHg (SD ± 53.1). This again indicates that in this study the compartment pressures were high which gave rise to low perfusion pressures.

The finding of blood within the subcutaneous tissue of an animal in the intramuscular haematoma group, animal 10, was associated with a high StO_2 value in this animal. A clinical situation could present in a similar fashion. The subcutaneous blood is not visible through the skin and could arise as a result of the initial injury. The NIRS monitor might then be placed over the area in question and a falsely elevated value of 80 or 90% StO_2 could be obtained. The high reading in the presence of a developing acute compartment syndrome would lead to a false negative diagnosis and place the patient at increased risk of sequaelae of compartment syndrome. The sensitivity of NIRS to collections of blood has already been used in the location of intracranial haematoma (Gopinath *et al.,* 1993).

The addition of the subcutaneous haematoma had two main effects; firstly the StO_2 increased from the baseline for StO_2 measured both over 12 mm and over 25 mm and secondly, the variability over 25 mm increased in contrast to that at 12 mm where the values recorded became steadier. The StO_2 value is calculated from the ratio of the concentrations of oxygenated and deoxygenated haemoglobin. The blood used for the 25 ml haematoma was taken from the blood transfusion bag that had been stored overnight. The purpose for this was to allow the blood gas concentrations of the haematoma blood to stabilise so that it could be measured. The pO_2 value obtained from the invasive monitor recording of the infusion blood used in the IM haematoma group indicated that pO_2 of the subcutaneous blood had a mean value of 85 mmHg. This value indicates that the haematoma blood was relatively well

oxygenated. Jobsis (1977) determined that near-infrared light is absorbed in the region of 830 nm by well-oxygenated tissue and the absorption disappeared almost completely under anoxic conditions. The presence of the haematoma superficial to the muscle is likely to have absorbed a significant proportion of the near-infrared light thus altering the ratio and producing an increased StO_2. Both the 12 mm interface and the 25 mm interface would have been affected by the increased absorption of the haematoma. The difference in the variability of the recordings for the two interfaces is likely to relate to the depth of penetration of light, the interoptode separation and the size of the haematoma. The interface that measured over 12 mm depth would have had a greater proportion of the light pathway within the superficial tissues where the haematoma was lying and as it has an interoptode separation of only12 mm the light pathway would have been more centrally located over the haematoma. This is likely to have produced almost total absorbance by the haematoma and therefore an elevated StO_2 value that remained steady (Figure 41b). The interface measuring over 25 mm depth has an optode separation of 25 mm. The haematoma was created with only 25 ml of blood and therefore light may be scattered through some tissue where the haematoma was dense and scattered through some tissue at the edge of the haematoma that was more normal. It is possible that the scattering of light through these tissues, which have variations in their absorbance of near-infrared light, is responsible for the variability seen in the tracing acquired over 25 mm in association with the subcutaneous haematoma (Figure 41a).

An intra-muscular haematoma was created by the infusion of whole blood into the centre of the muscle compartment. The blood used for the intra-muscular haematoma was prepared in the same manner to that which was used for the subcutaneous haematoma. The collection of blood within the muscle had a mean

volume of 56 ml, twice that of the subcutaneous haematoma, yet the StO_2 correlated in a similar fashion to that of the plasma infusion only animals. Both the 25 mm and 12 mm interfaces penetrate tissues according to their respective inter-optode distance (Inspectra™ Tissue Spectrometer, Hutchinson Technology Incorporated, USA). The receiving optode collects light that has been reflected from tissue throughout this depth and not just from the tissue at a depth equivalent to the inter-optode distance. Light travelling through biological tissues is scattered throughout the illuminated field and therefore light can travel to the receiving optode having only been reflected by very superficial tissue. Fifty percent of the StO_2 signal for the 25 mm interface is derived from the most superficial 50% of tissue (personal communication with Hutchinson Technology Incorporated, USA). This corresponds to the superficial 12.5 mm of tissue. The ultrasound scanning has indicated that the mean depth of anterior compartment muscle was 16.7 mm and the subcutaneous tissue was 4.7 mm. If the IM haematoma lies at the centre of the muscle then there would be a mean of 13.1 mm (16.7 mm/2 + 4.7 mm) of superficial tissue without haematoma, and therefore would provide more than 50% of the signal for the 25 mm interface and the entire signal for the 12 mm interface. It is expected that this upper region of muscle would become hypoxic in response to the increase in compartment pressure, irrespective of whether this is generated by a plasma or whole blood infusion. This in part explains why the IM haematoma group (group 3) behaved so similarly to the plasma infusion group (group 1), however some near-infrared light would still be expected to travel into the haematoma. Near infrared light will penetrate tissue corresponding to the intensity of light and therefore is unable to differentiate the origin of haemoglobin. Prior to infusion the whole blood had a mean pO_2 of 84.7 mmHg, whereas at loss of twitch the mean pO_2 of the compartment was 38.0 mmHg. The high level of carbon

dioxide in the pressurised compartment is likely to assist in unloading the oxygen from the red cells in the blood infusion to the hypoxic tissues (the Bohr effect). This would thereby reduce the oxygen concentration in the IM haematoma. If the oxygen concentration of the haematoma equalises with the hypoxic muscle tissue then the absorbance of the two tissues would be similar and the StO_2 of the portion of the IM haematoma would be similar to that of the surrounding muscle in the light pathway. The depth of the intramuscular haematoma and loss of oxygen to the surrounding tissue could explain the similarity of the results for the plasma only and intramuscular haematoma groups.

The recovery of the StO_2 to near normal levels following the fasciotomy was more rapid in the plasma only infusion group (group 1) compared to the intramuscular haematoma (group 3) animals. Invasive pH, pO_2 and pCO_2 monitoring has demonstrated that the intramuscular pCO_2 in group 3 animals was significantly lower at the point of loss of twitch. The measurement of these values within the infusions indicated that the whole blood had a lower, but not significant, pH, and pO_2 and greater pCO_2 than the plasma infusions. This may possibly have influenced the intramuscular environment thus leading to a slower recovery following the fasciotomy.

The porcine acute compartment syndrome models (Garr *et al.*, 1999; Arbabi *et al.*, 1999) did not report any confirmation that the StO_2 changes observed reflected the intramuscular metabolic environment. Nuclear magnetic resonance (NMR) technology has demonstrated that NIRS can indicate the desaturation of haemoglobin and myoglobin in human calf muscle as effectively as NMR (Tran *et al.,* 1999). In this study however, the use of the invasive pH, pCO_2 and pO_2 monitor has allowed metabolic changes within the muscle compartment to be identified alongside non-

invasive StO_2 changes. The pH, pCO_2 and pO_2 monitor has been evaluated previously in clinical studies examining continuous arterial blood gas sampling (Venkatesh *et al.,* 1994) and cerebral tissue gas estimation during craniotomy for cerebrovascular surgery (Hoffman *et al.,* 1996). Intramuscular pO_2 has been shown to be more sensitive to microcirculatory changes than compartment pressure in an ischaemia-reperfusion rat model (Seekamp *et al.,* 1997). An invasive optical pH, pCO_2 and pO_2 sensor, similar to the one used in this study, has demonstrated that intramuscular metabolite changes reflect systemic blood metabolite concentrations in response to haemorrhage and resuscitation in dogs (McKinley *et al.,* 2000). This canine study demonstrated a rapid fall in pO_2 (30 mmHg to 10 mmHg over 15 minutes) compared to the steady fall in pH and rise in pCO_2 that occurred over 75 minutes before the dogs were resuscitated. Following the resuscitation, the pO_2 increased to above the baseline and the pH and pCO_2 improved with time but did not did reach normal values at 5 hours after the resuscitation. The intramuscular variations in metabolites that were seen in response to systemic hypoperfusion and resuscitation mimic those that were observed in this compartment syndrome model in response to the increase in intramuscular pressure and subsequent fasciotomy (Figure 52). It is possible that the monitoring of more than one intramuscular parameter, as has been carried out with this invasive monitor, could provide not only an accurate measure of the metabolic state of the muscle, but also provide a better indication of where in time the measurement has been taken during a developing problem within the muscle due to the different rates of change of the metabolites.

The design of this study was restricted by the availability of the pH, pCO_2 and pO_2 monitor, in that only one monitor stack could be provided. This meant that there are no true control values for pH, pCO_2 and pO_2 from the contralateral limbs without

compartment syndromes. The inferences that have been made with respect to pH, pCO_2 and pO_2, have been by referencing against the baseline value taken at the beginning of the experiment. This process appears to be standard practice in other animal studies involving intramuscular monitoring (McKinley *et al.,* 1998; Seekamp *et al.,* 1997). The results for this porcine study indicate the possibility of systemic arterial blood gas changes over the course of the experiment. This indicates that there was a need for a control invasive pH, pCO_2 and pO_2 monitor in the contralateral limb.

In this porcine model the peripheral intramuscular temperature was recorded as well as the central temperature as the previous porcine studies (Garr *et al.*, 1999; Arbabi *et al.,* 1999) only recorded and maintained central temperature at 38°C using a heated table. The sub-cutaneous haematoma group was found to have a significantly higher core and peripheral intramuscular mean temperature throughout the duration of the experiment. Physiological responses to core and peripheral temperature have the ability to affect blood flow to the skin. Experiments involving forearm immersion in water of different temperatures did not influence NIRS recordings in the wavelengths 760 – 800 nm (Mancini *et al.*, 1994). A comparison of NIRS and transcutaneous oxygen after the release of a tourniquet indicated a rapid rise in the NIRS signal relative to the transcutaneous oxygen. The transcutaneous oxygen did not show evidence of a reactive hyperaemia which suggests that NIRS is more strongly influenced by oxygen sufficiency in deeper tissues (Hampson and Piantodosi, 1988).

Discussion points have been raised with regard to NIRS in acute compartment syndrome concerning the influence of oedema that may form in the subcutaneous tissues (Garr et al., 1999), but there was no evidence on how much oedema would be expected and over how long the observations would need to be made. The oedema fluid would not be expected to absorb light at the wavelengths used (Boushel and

Piantadosi, 2000). With the use of ultrasound scanning it has been possible to quantify the degree of swelling that occurred during the development of an acute compartment syndrome in this model. It has been shown that there was not a significant degree of swelling and so the StO_2 changes that were observed could not be secondary to the development of oedema in the subcutaneous tissues. This model however, has not been able to determine whether an oedematous limb with normal perfusion has the same StO_2 value as a non-oedematous normally perfused limb.

This animal model has allowed observations to be made into the effect on NIRS of the skin and subcutaneous tissue overlying muscle that has not been injured by an acute compartment syndrome. A human volunteer study, published during the experimental period, suggested that an increase in adipose tissue thickness was associated with a decrease in the StO_2 value recorded by NIRS (van Beekvelt *et al.*, 2001). When the skin and subcutaneous tissue was dissected free to become ischaemic, the value of StO_2 changed very little. This is in keeping with the belief that the contribution from the haemoglobin within this layer is small (Mancini *et al.*, 1994; Hampson and Piantadosi, 1988). When the interface was placed directly on the muscle the value rose by at least 10%. This suggests that the presence of a layer of skin and adipose tissue reduces the StO_2 value in a similar fashion to that demonstrated in human volunteers (van Beekvelt *et al.*, 2001). This conclusion would need to be validated in a larger study over muscle of greater depth because the removal of the skin and subcutaneous tissue allows the 25 mm interface to potentially begin to pick up signal from the bone beneath the muscle compartment and therefore this could be the source of the increase in StO_2. Although not confirmed, it is felt that any contribution to the increase from bone is unlikely as the increase in StO_2 on removal of the skin and subcutaneous tissue was also observed using the 12 mm

interface. The volunteer study of this thesis demonstrates similar values recorded over the midpoint of the tibia and anterior compartments at rest.

The ischaemia to the pig hind limb was caused by direct occlusion of the common femoral artery, as it was not possible to apply a tourniquet due to the conical shape of the limb. The clamp was left in place for 15 minutes to allow the StO_2 to change and stabilise before any values were recorded. The StO_2 value fell approximately 50% at 25 mm and 30% at 12 mm when measured directly over muscle. In human volunteers, tourniquet experiments have demonstrated a decrease in muscle oxygenation using NIRS down to 28 (± 9)% from a baseline of 74 (± 6)%. This gave a decrease of 46% over the observation time of 20 minutes to reach steady state (Muellner *et al.,* 1999). The decrease was similar in this experiment following the arterial occlusion, but not as great as had been seen during the compartment syndrome model where the reductions were 60% and 35% respectively. A tourniquet experiment provides useful information on the physiological responses to acute ischaemia, but this study has reinforced the fact that the de-oxygenation in an acute compartment syndrome is 'more severe' due to the combined effects of ischaemia and pressure (Heppenstall *et al.,* 1986).

The mean StO_2 value at 12 mm when the interface was directly applied to ischaemic muscle was found to be 60 (± 12)% compared to 46 (± 16)% for the 25 mm interface after 15 minutes of arterial occlusion. This difference was not significant with numbers involved, but a significant difference was found when the ischaemic skin was replaced. As there had been no difference between the interfaces when they were applied to ischaemic skin and healthy muscle, it is reasonable to assume that difference is due to a change within the muscle. As the arterial inflow has been occluded, maximal oxygen will be shifted from the capillaries to the tissues. It is

known that 70% of the haemoglobin contributing to the absorbance of NIRS is located within the venous side of the capillary network (Boushel and Piantadosi, 2000). As the interfaces are sending light to different depths of the muscle, the more superficial part of the muscle may have better preserved oxygenation relative to the deeper tissues where there is a greater concentration of post-capillary venules containing more de-oxygenated haemoglobin.

Garr *et al.* (1999) reported a significant negative correlation between compartment pressure and StO_2 ($r = - 0.78$, $p < 0.001$). In the plasma infusion only (group 1) animals in this study, the correlation was very similar ($r = - 0.7$, $p < 0.01$). Garr *et al.* (1999) suggested that further investigations into the ability of NIRS to detect an acute compartment syndrome in a severe injury model were warranted. This study has reproduced the porcine model with a similar degree of correlation and shown that the relationship is lost in the presence of a subcutaneous haematoma, a common finding in a severely injured limb.

4 VOLUNTEER STUDIES

4.1 Introduction

The clinical study investigated the ability of a non-invasive near-infrared spectrometer to correlate with intra-compartmental pressure changes in an acute compartment syndrome. The study indicated that the soft tissue oxygenation (StO_2) only correlated weakly with intra-compartmental pressure in patients, contrasting to the promising results suggested from earlier animal studies (Garr *et al.,* 1999; Arbabi *et al.,* 1999). The correlation was improved by calculating the StO_2 difference between two legs to reduce the effect of inter-patient variability for baseline values. The animal model described in this thesis has identified one factor, the subcutaneous haematoma, which could lead to a false negative diagnosis of an acute compartment syndrome. The clinical study demonstrated that there were significant differences between male and female patients with regard to the StO_2 values on the uninjured legs. Differences were also identified between male and female subjects with regard to the distance between the skin surface and the fascial compartment.

Near-infrared light is affected by the thickness of the subcutaneous tissue and near-infrared light itself has been used to help in the determination of body composition. Optical density, using near-infrared light, can be calculated and has been found to correlate linearly with the fat thickness over the biceps and total body adipose content (Heyward *et al.,* 1992). The prediction of composition using NIRS, however, has not improved on the accuracy of taking skin fold thickness measurements and using race specific equations.

The interpretation of NIRS and the measurement of tissue oxygenation depend on the accurate identification of possible patient influences on the output value. The volunteer studies described in this section investigate the relationship between soft tissue oxygenation, measured by near-infrared spectroscopy and soft tissue composition in the human leg.

4.2 Materials and Methods

Ethical committee approval for an investigation into the relationship between soft tissue oxygenation, measured by near-infrared spectroscopy and soft tissue composition was sought and granted from the Lothian Research Ethics Committee before recruitment was started (Appendix I).

Study design and subject selection

This investigation was carried out as two sequential studies to examine the relationship between soft tissue oxygenation and soft tissue composition in normal volunteers. Both studies recruited male and female volunteers employed by The Lothian University Hospitals Trust, from within the Orthopaedic and Accident and Emergency Departments. Recruits to the studies were not randomised, as these studies did not attempt to establish a normal range, but investigated correlations within individuals. Initially 100 volunteers (equal male and female) were recruited to investigate the relationship between soft tissue oxygenation measured over 25 mm and the distance between the skin and fascia covering the muscle. The second volunteer study involved 26 volunteers (equal male and female) and used a similar protocol. The second study tested NIRS interfaces that measured 12 mm, 25 mm and 35 mm in depth.

Written consent, for both studies, was obtained after an explanation, given by the author, of the investigational device and the procedure.

Exclusions.

1) Volunteer subjects with an age of less than 16 years.

2) Subjects with a known history of diabetes mellitus, cardio-respiratory or peripheral vascular disease.

3) Subjects with a past history of operative procedures in the region to be monitored.

Investigational device.

The InSpectra^{TM} Tissue Spectrometer (Hutchinson Technology Inc (HTI), Hutchinson, Minnesota, USA) that was used in both the clinical and animal studies was again used as the investigation device in this study.

In the first of the two volunteer studies the interface with a distance between the sending and receiving optodes (inter-optode distance) of 25 mm was used. This provided tissue saturation data over 25 mm depth from the skin surface (Hutchinson Technology Inc (HTI), Hutchinson, Minnesota, USA). The second study compared the values obtained from interfaces with inter-optode distances of 12 mm, 25 mm and 35 mm. The inter-optode distance is proportional to the depth of measurement in the tissues. In this second study it was possible also to collect data on the total haemoglobin within the light pathway of the 25 mm interface. The second study investigated the effect of varying the inter-optode distance on the correlation between the skin to fascia distance and StO_2.

Data collection.

The following data was collected on each volunteer:

Date of birth, and sex

Height (m) and weight (kg)

Blood pressure and pulse oximetry

Standard skin fold thickness (cm) (triceps, biceps, scapula and iliac crest)

Skin fold thickness over anterior tibial compartment (cm)

Calf circumference 10 cms distal to the tibial tuberosity (cm)

Mid upper arm circumference (cm)

Skin fold thickness

In addition to the use of ultrasound to determine the soft tissue composition in the lower leg, skin fold thickness was measured over the lower leg and in a standard fashion over the four recommended sites (Thomas, 1994) using a pair of Harpenden skinfold calipers (Appendix J). The purpose of obtaining measurements of skin fold thickness over the lower leg, standard skin fold thickness and calf circumference was to determine if a correlation existed with the ultrasound measurements of adipose thickness over the lower leg. Calculation of total body fat was made from standard skinfold thickness (Durnin and Wormersley, 1974). Should a correlation exist between the StO_2 and the ultrasound measurements of adipose layer thickness, then a correction factor for the adipose thickness of the lower leg would be required. Rather than requiring to carry out an ultrasound scan of every patient leg, if a correction to the StO_2 value could be made using other patient parameters, such as height, weight, skin fold thickness or calf circumference then the process could be simplified.

Subject position.

The subjects were positioned on a couch in a sitting position with legs outstretched (hips flexed to 45 degrees and knees extended) to represent the position of patients in ward beds thereby allowing comparison with results obtained form the clinical study. This position was maintained for five minutes prior to depth and StO_2 measurements to allow any influence of venous pooling due to previous upright position to be minimised. All recordings were carried out in the same room during a period between 13.00 and 14.30 hrs.

Near-infrared spectroscopy measurements.

Study 1. StO_2 values were recorded for 100 volunteers over the following sites (Figure 6) using the 25 mm NIRS interface:

5 cm distal to tibial tuberosity and 2 cm lateral to subcutaneous border of tibia (right leg).
5 cm distal to tibial tuberosity and 4 cm lateral to subcutaneous border of tibia (right leg).
10 cm distal to tibial tuberosity and 2 cm lateral to subcutaneous border of tibia (right leg).
10 cm distal to tibial tuberosity and 4 cm lateral to subcutaneous border of tibia (right leg).
10 cm distal to tibial tuberosity and 2 cm medial to subcutaneous border of tibia (right leg).
10 cm distal to tibial tuberosity and 2 cm lateral to subcutaneous border of tibia (left leg).

The measurement of StO_2 to the medial side of the subcutaneous border of the tibia was included to observe NIRS over bone.

Study 2. StO_2 values were recorded for 26 volunteers over the same sites as in study 1, but using interfaces with inter-optode distances of 12 mm, 25 mm and 35 mm. The 25 mm interface also collected the data for the total haemoglobin in the light pathway.

Soft tissue composition measurements.

Ultrasound scans were carried out using a portable scanner that was the same as the one used in the clinical and animal studies (Sonosite™ 180, Sonosite Inc., Bothel, Washington, USA; supplied by Medical Supplies (UK)). The depth measurements of skin to deep fascia and anterior compartment depth (Figure 20) were made at the same sites as the recordings for StO_2 for both volunteer studies. The scan over the tibia only measured the distance between the skin surface to periosteum. The scan was sufficiently detailed to also allow a recording of the skin thickness. This was carried out at 10 cm distal to tibial tuberosity and 2 cm lateral to SC border of tibia (right leg).

Statistical Analysis.

The data was initially screened for normality. Statistical analysis was performed to assess the degree of correlation between the non-invasive StO_2 measurements provided by the InSpectra™ Tissue Spectrometer and the depth of soft tissues using Spearman's rho test for non-parametric data. Correlations between soft tissue thickness and other subject parameters have been analysed. Differences between sexes are analysed using independent samples tests. All data are reported as means ± SD. The level of statistical significance was set at $p < 0.05$.

4.3 Results - Study 1.

Fifty male and fifty female volunteers were recruited. Mean age was 32 (± 11) years. Table 32 shows the baseline data for all volunteers as a whole and also divided into male and female groups. The recruitment of subjects was influenced by the local population bias in the hospital department and therefore an age difference of 5.3 years was present between the sexes. This difference was not significant with the numbers recruited. Significant differences between the genders were found with regard to height, weight, and Body Mass Index. Systemic blood oxygen saturation, measured by pulse oximetry was found to be significantly higher in women ($p < 0.01$).

	All		Male		Female		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Significance**
Age (years)	32.4	±11	29.8	±10	35.1	±12	$p = 0.06$
Height (m)	1.70	±0.1	1.77	±0.06	1.63	±0.08	$p < 0.01$
Weight (kg)	71.4	±14.9	78.5	±11.5	64.4	±14.8	$p < 0.01$
BMI	24.7	±4.8	25.2	±3.7	24.2	±5.6	$p < 0.05$
diastolic BP (mmHg)	83	±11	83	±10	82	±12	$p = 0.38$
Pulse oximetry (%)	97.8	±1.6	97.5	±1.5	98.2	±1.6	$p < 0.01$
smoker	26%		24%		28%		$p = 0.39$

Table 32 Study 1 - Mean (±SD) baseline values for age, height, weight, Body Mass Index (BMI), diastolic blood pressure, systemic oxygen saturation and proportion of smokers for all volunteers, and divided by sex (Mann-Whitney U test).

NIRS and adipose tissue thickness measurements over muscle

The mean value of StO_2 over the anterior leg was 71% (±21). For a male the mean StO_2 was 81% (±12), whereas for a female this was 61% (±22); the difference was significant ($p < 0.01$). The mean distance between the skin surface and the fascia measured using the ultrasound scanner was 0.56 cm (±0.24). A significant difference was also detected between the sexes ($p < 0.01$), where the mean distance for a male was 0.43 cm (±0.15) and for a female this was 0.69 cm (±0.25). The data has been screened for normality and was positively skewed (Figure 55). The distance between the skin surface and the fascia has been plotted with the corresponding StO_2 value measured using the 25 mm interface (Figure 56). Each point represents a single site of measurement. The four sites over the anterior muscle compartment from the right leg of each subject have been represented individually without using mean values to ensure that any correlation is not overlooked. Figure 56 indicates that the relationship between the skin surface to fascial distance and StO_2 is linear and significantly negatively correlated for both men and women (Spearman's rho correlation = - 0.72). There was no significant difference in the slope of the lines for the two sexes. The equation representing the linear model for the relationship between the skin surface to fascial distance and StO_2 is:

$$\mathbf{StO_2 = a + b * skin\ to\ fascia\ distance}$$

Where a = 108.7 and b = - 67.4, constants predicted from the linear model (Figure 57).

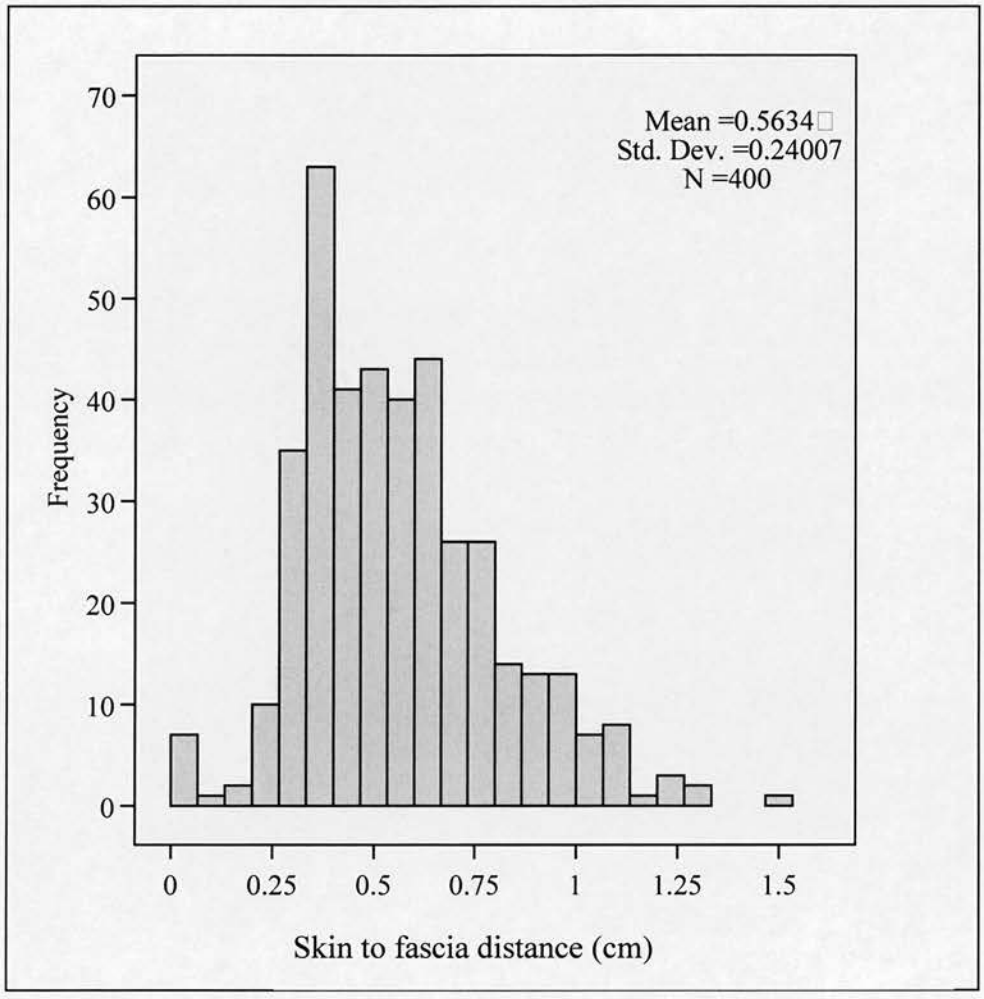

Figure 55 Histogram of the skin to fascia distance over 400 sites, 4 in each individual. The data is positively skewed and therefore not normally distributed. (Skewness: 0.699 (SE 0.122); Kurtosis 0.586)

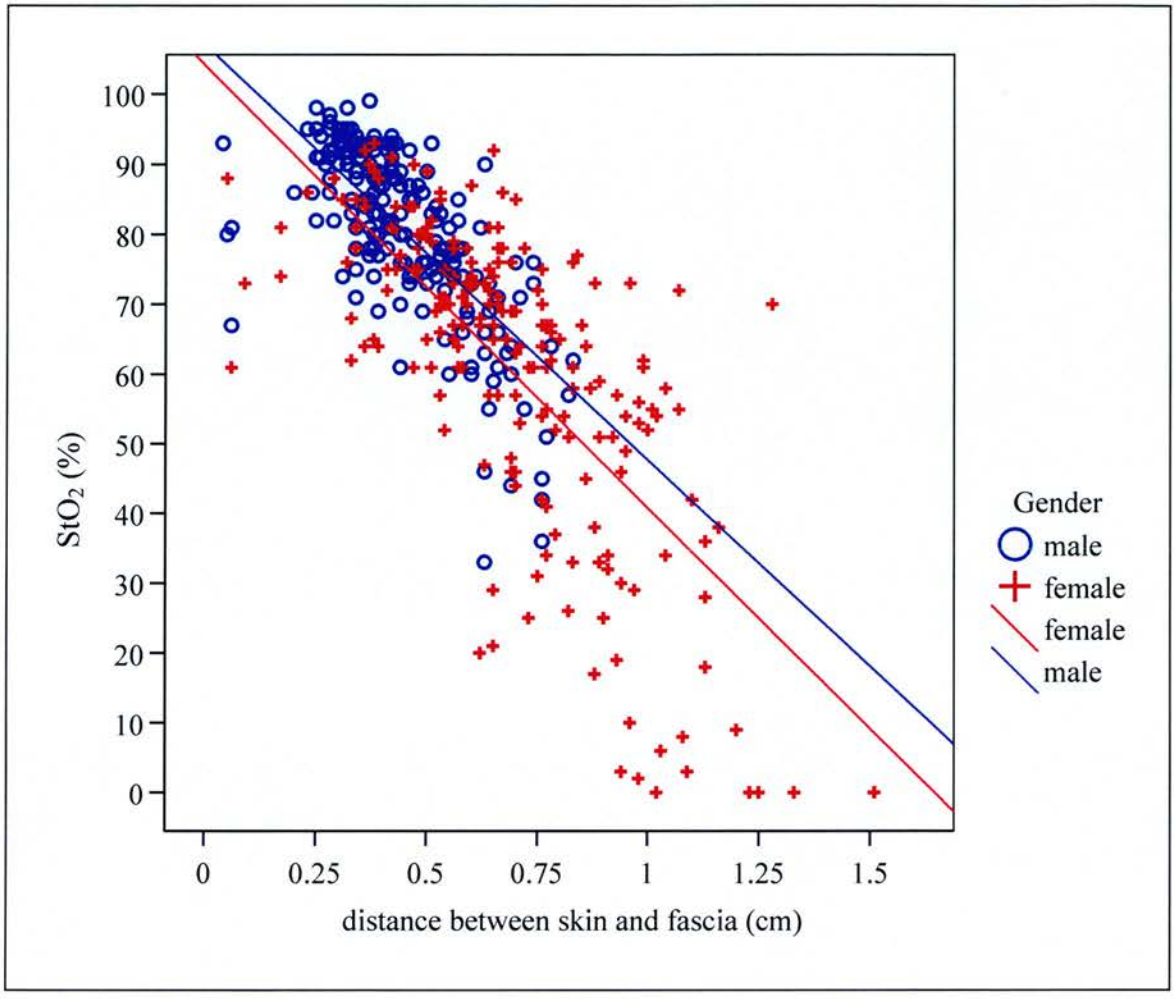

Figure 56 StO_2 (%) over 25 mm depth from the anterior compartment of the leg plotted against distance between skin and fascia (cm) at the same sites. Lines represent linear correlation for male and females. Correlation male = - 0.723, $p < 0.01$, female = - 0.720, $p < 0.01$ (Spearman's rho).

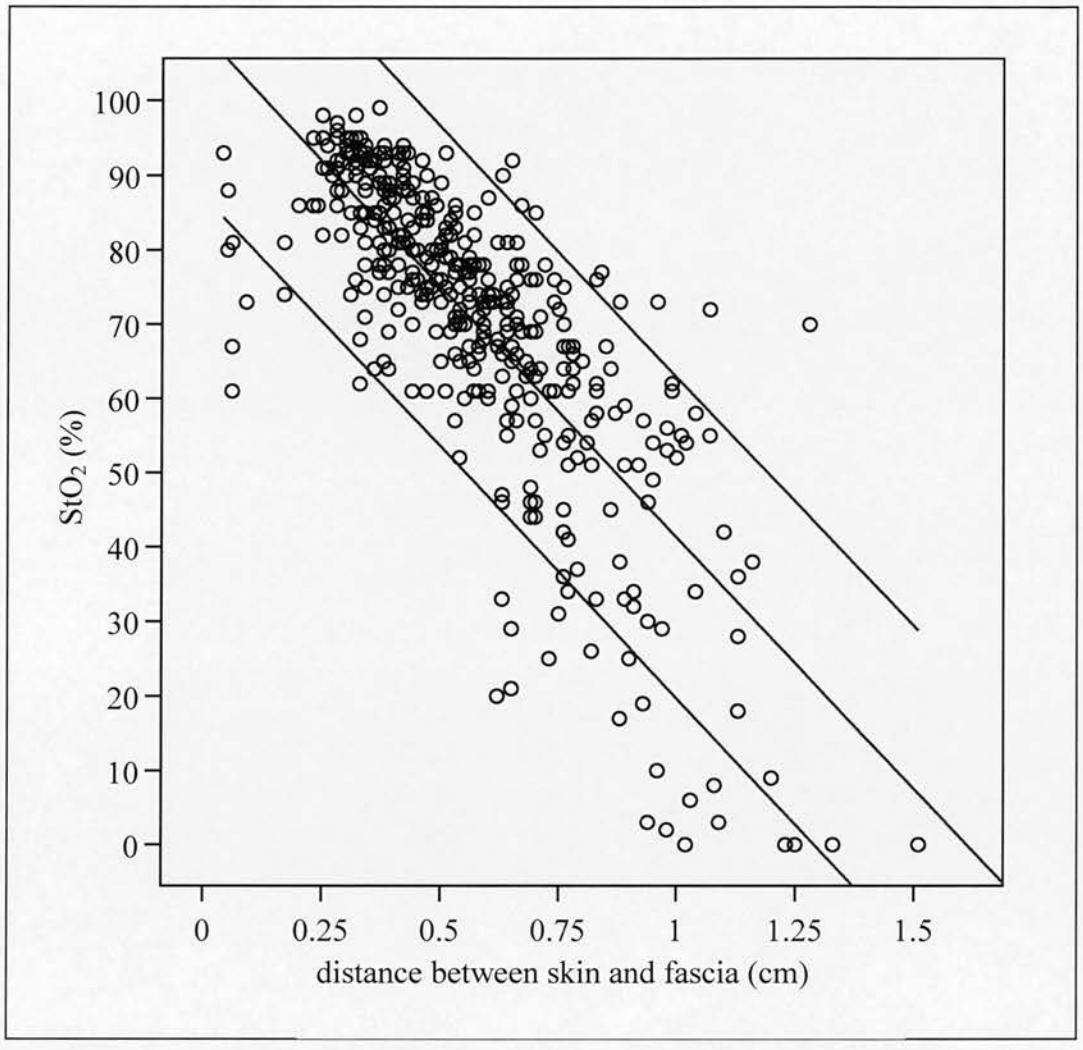

Figure 57 StO_2 (%) over 25 mm depth from the anterior compartment of the leg plotted against distance between skin and fascia (cm) for all subjects. Central line (with 95% confidence intervals, outer lines) represents linear model: $StO_2 = a + b^*$ *skin to fascia distance*, a and b are constants.

NIRS and skin thickness measurements

The distance between the skin surface and the fascia contains adipose tissue and the skin itself. The resolution of the ultrasound scan allowed the measurement of the thickness of the skin, from the surface to the junction between the dermis and the adipose tissue (Figure 58). The mean skin depth over the anterior leg was 0.15 cm (±0.02), for a man the mean value was 0.15 cm (±0.02) and for a woman the mean was 0.14 cm (±0.02). There was little variation between subjects and no statistical difference between the sexes with regard to skin thickness ($p = 0.1$).

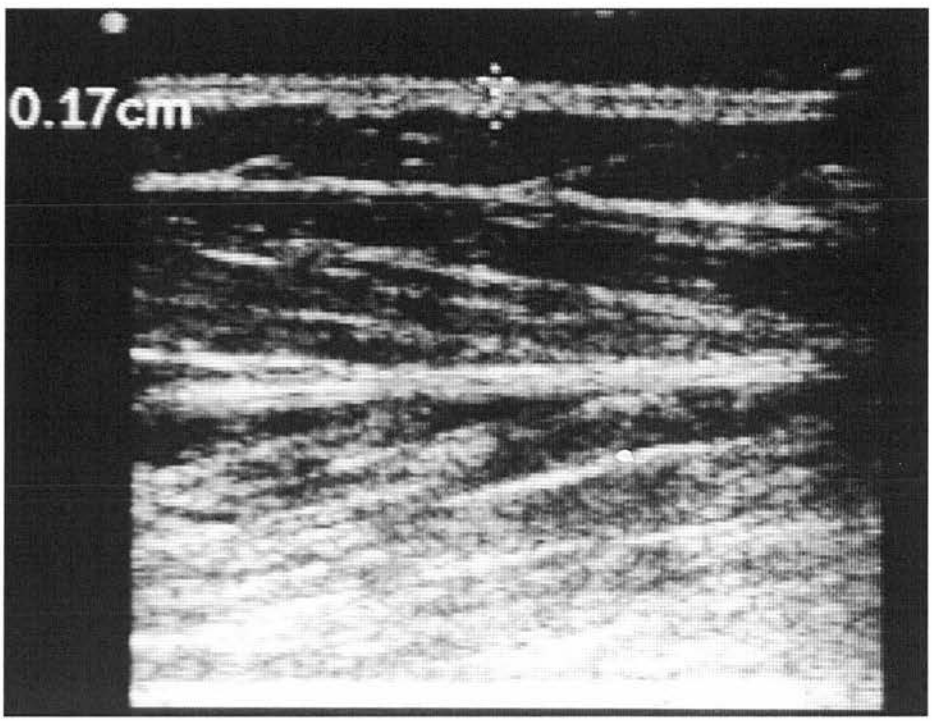

Figure 58 Ultrasound image of the anterior compartment of the leg indicating the resolution of the scan to allow measurement of the skin thickness (cm).

NIRS and muscle compartment thickness measurements

Included within the 25 mm depth influencing the StO_2 value is also the muscular compartment. It was possible to record the distance between the anterior and posterior fascia of the tibialis anterior muscle. Mean distance from anterior to posterior fascia was 1.29 cm (±0.34). No significant correlation was found between the StO_2 and the distance between the anterior and posterior fascial layers covering the tibialis anterior muscle. It should be noted however, that the tibialis muscle is approximately cylindrical in section and if a cylinder is divided at different sites parallel to the longitudinal axis, the distance between the upper and lower surfaces of will vary and therefore a range of values will be recorded. The posterior margin of the anterior compartment was not clearly identified with the ultrasound scan. The scan was clearly able to identify that the deeper tissue had the striated appearance of muscle and therefore no further changes to the soft tissue composition were expected deep to the tibialis anterior muscle.

NIRS and adipose tissue thickness measurements over bone

When the StO_2 was recorded over the tibia the mean value for a man was 79% (±16.9) and for a woman was 60% (±23.5). The difference was significant ($p < 0.01$). The depth of soft tissue overlying the bone was again found to correlate with the StO_2 over 25 mm depth (Figure 59).

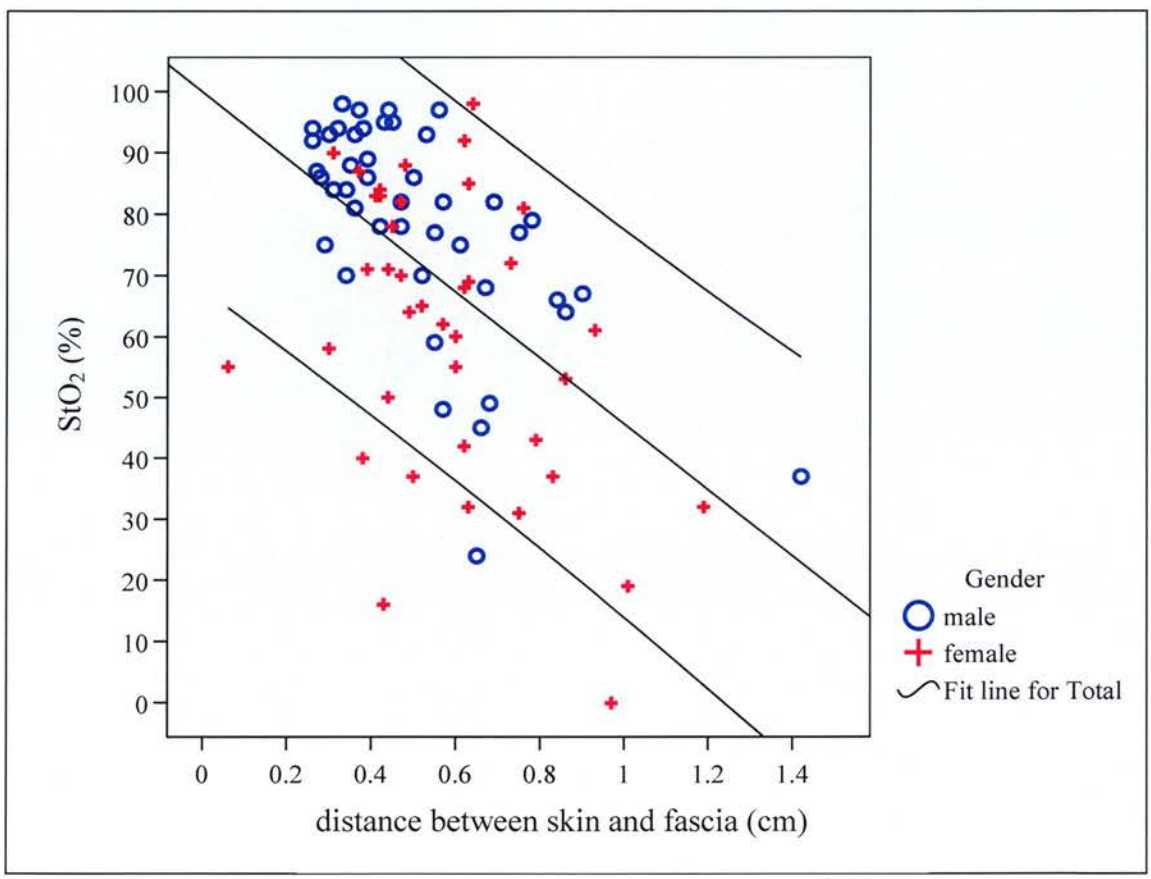

Figure 59 StO_2 (%) over 25 mm depth from over the tibia plotted against distance between skin and fascia (cm). Linear correlation (and 95% confidence interval) displayed (Spearman's rho correlation coefficient = -0.55, $p < 0.01$). There was no significant difference in slope of correlation for males and females.

NIRS and adipose tissue thickness difference between each leg

The clinical study reduced the inter-patient variability by comparing the injured and uninjured legs. This volunteer study compared both legs at the same site as that used in the clinical study (10 cm distal to tibial tuberosity and 2 cm lateral to sub-cutaneous border of tibia). The mean StO_2 values for a man were 84.0% (±10.1) on the left and 83.8% (±8.6) on the right ($p = 0.8$). The corresponding mean distances between the skin surface and the fascia were 0.43 cm (±0.13) on the left and 0.38 cm (±0.12) on the right ($p < 0.01$). The women had mean StO_2 values of 69.8% (±16.2) on the left and 70.4% (±14.9) on the right ($p = 0.7$). The women also showed a slight difference in the skin to fascia distance, but this was not significant. The mean distances were 0.61 cm (±0.25) on the left and 0.58 cm (±0.20) on the right ($p = 0.23$). The dominant side of each volunteer was not recorded.

The influence of age on NIRS and adipose tissue thickness

The male and female groups were known to differ significantly in age due to population bias in the hospital population from which the sample was drawn, therefore the skin to fascia distance or adipose thickness (AT) has been plotted with the age of the subject to identify any age related trends. No significance difference between the sexes was found (Figure 60). Systemic saturation, measured by pulse oximetry, was significantly higher in female subjects (Table 32). There was no significant correlation however, between systemic saturation and StO_2 in men or women (correlation coefficient, male = 0.07, $p = 0.66$; correlation coefficient, female = - 0.26, $p = 0.07$). The StO_2 values over 25 mm were found to correlate with the Body Mass Index for men (correlation coefficient, male = - 0.62, $p < 0.01$), but not for women (correlation coefficient, female = -0.18, $p = 0.21$).

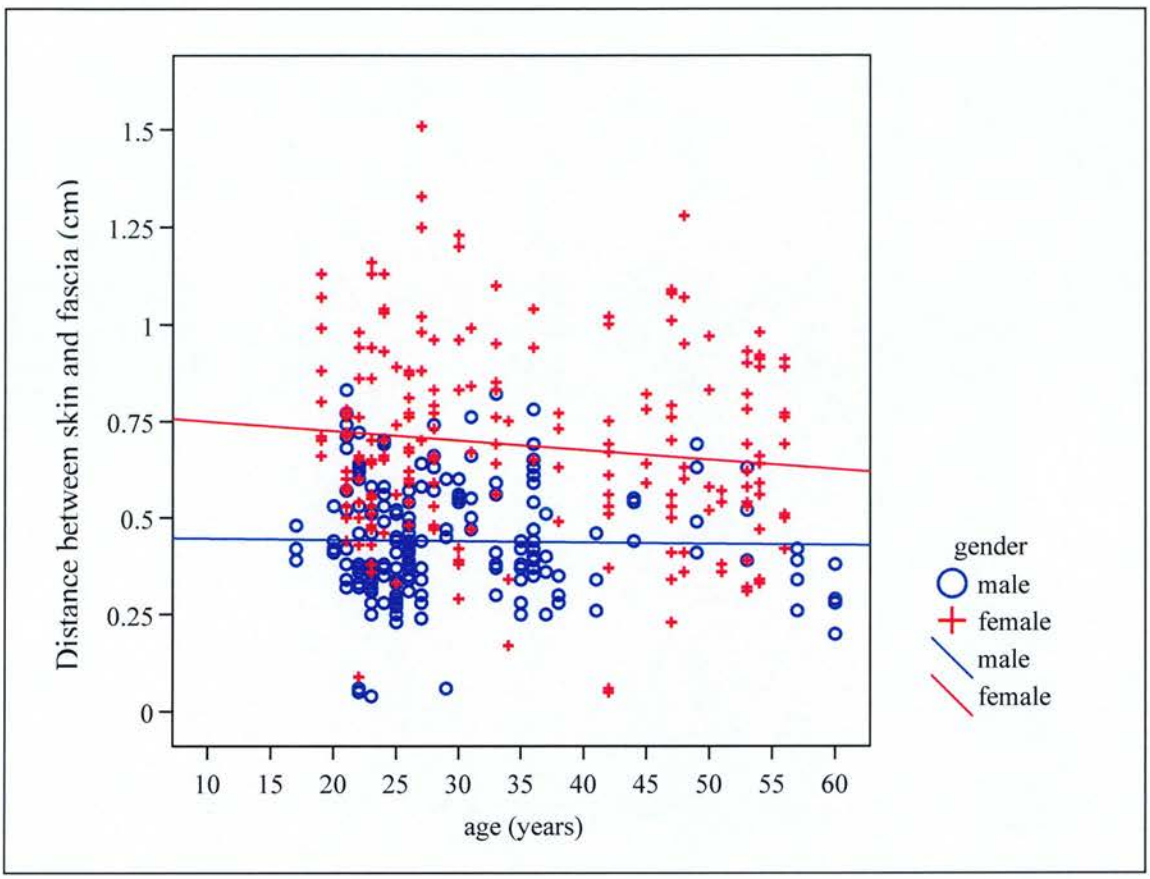

Figure 60 Age (years) and distance between skin and fascia (= adipose thickness, cm) compared for male and female subjects. There was no significant difference between the two groups.

The effect of smoking on NIRS and adipose tissue thickness

The mean values of StO_2 over the anterior leg compartment, skin to fascia distance and age were compared for smokers and non-smokers. Male smokers were significantly older (37 years ±10 and 27 years ± 9 for non-smokers, $p<0.01$), but no difference was found with regard to the StO_2 where the mean value was 80.1% for both smokers and non-smokers. There was no significant difference in the mean skin to fascia distance between smokers and non-smokers of each sex (males: 0.42 cm ± 0.11 and 0.46 cm ± 0.13, $p = 0.4$; females: 0.71 cm ± 0.18 and 0.67 cm ± 0.21, $p = 0.5$). Female smokers were younger, but

not significantly (mean age 33 years ±12 and 36 years ± 13 for non-smokers, p = 0.6). The mean StO_2 value for a female smoker was 56.1% (±17.6), compared to 62.5% (± 18.6) for a non-smoker (p = 0.2)

Skinfold thickness measurements

This study has demonstrated a significant relationship between the NIRS measurement and the adipose thickness. Skin fold thickness measurements were made on all subjects to identify a potential predictor for the adipose thickness over the anterior leg. Table 33 details the correlation coefficients between the anthropomorphic measurements and the adipose thickness (AT) over the leg (10 cm distal and 2 cm lateral to the tibial tuberosity, measured by ultrasound scanning). The total body fat was calculated according to the sum of the skinfolds and the conversion table accounting for age (Durnin and Wormersley, 1974). The values for 'skin fold thickness' have been divided by two in order to provide a measure of a single layer of skin and adipose tissue. The only significant correlations, in both men and women, occurred between leg AT and the biceps skinfold thickness and the skinfold directly over the leg. The closest correlation however, was with the skin fold measurements made directly over the lower leg (Figure 61). The standard anthropomorphic measurements do not accurately predict the thickness of adipose tissue over the leg due to the variability in fat distribution, particularly in the female subjects in this study. In addition, the calf circumference did not predict the adipose tissue thickness (correlation = - 0.44). A useful predictor, elsewhere in the body, for the adipose thickness over the leg that could be used in calibration of the StO_2 has not been identified by this study.

	Male n = 50		Female n = 50	
	Correlation coefficient	**Significance**	**Correlation coefficient**	**Significance**
Height (m)	-0.16	$p = 0.28$	0.12	$p = 0.42$
Weight (kg)	0.31*	$p < 0.05$	-0.06	$p = 0.68$
BMI	0.40	$p < 0.01$	-0.19	$p = 0.19$
Calf circumference (cm)	0.38	$p < 0.01$	-0.44	$p = 0.76$
Upper arm circumference (cm)	0.28	$p < 0.05$	-0.07	$p = 0.62$
Iliac crest skin fold thickness (cm)	0.25	$p = 0.08$	-0.09	$p = 0.55$
Scapula skin fold thickness (cm)	0.46	$p < 0.01$	-0.08	$p = 0.60$
Biceps skin fold thickness (cm)	0.37	$p < 0.01$	0.39	$p < 0.01$
Triceps skin fold thickness (cm)	0.41	$p < 0.01$	0.16	$p = 0.28$
Total body fat (%)	0.35	$p < 0.05$	0.013	$p = 0.93$
Skin fold thickness 10 cm from tibial tuberosity (cm)	0.66	$p < 0.01$	0.72	$p < 0.01$

Table 33 Correlation coefficients (and significance) between adipose thickness at 10 cm distal and 2cm lateral from the tibial tuberosity (right leg) measured by ultrasound and measurements of leg and standard skin fold thickness and other anthropomorphic measurements (Spearman's rho test).

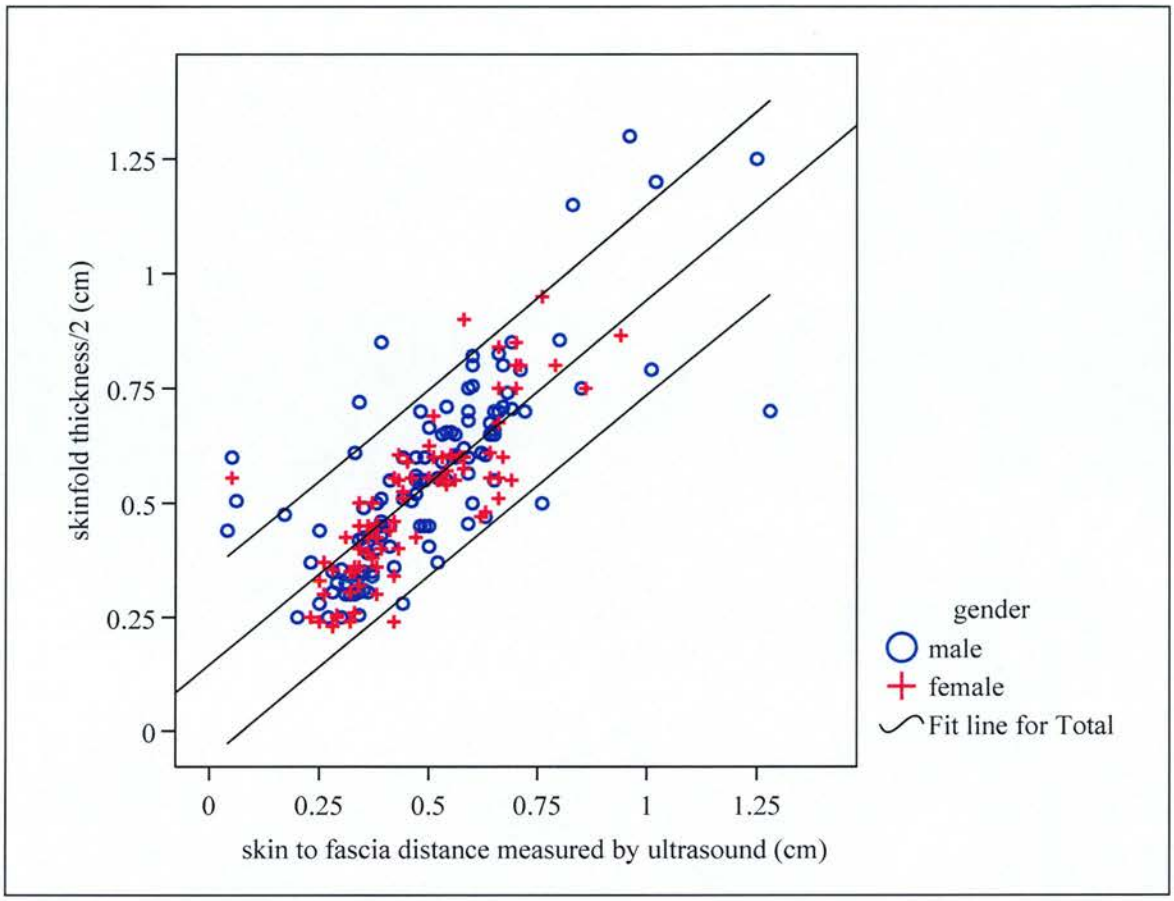

Figure 61 Skin to fascia distance (cm) (adipose thickness –AT) over anterior compartment at 5 cm and 10 cm from tibial tuberosity (right leg) measured by ultrasound (cm) plotted with corresponding skinfold measurement (cm) divided by two. Volunteers labelled by gender. Linear model displayed, with 95% confidence intervals. Correlation coefficient = 0.81, $p < 0.01$ (Spearman's rho test).

StO_2 has a linear relationship to the AT measured by ultrasound (Figure 61). Due to the close correlation of the ultrasound and skinfold measurement over the leg, StO_2 also correlated significantly with the skinfold measurement over the leg (Figure 62). There was no significant difference in the slope of the lines between the sexes. A linear equation therefore can be calculated for the expected normal StO_2 based on the skinfold measurement ($StO_2 = a + b*skinfold\ thickness/2$). The constants predicted from Figure 62 are $a = 108.5$

and b = -60.0. These values are similar to those predicted from the plot between StO_2 and the ultrasound measurements, a = 108.7 b = -67.4 (Figure 61).

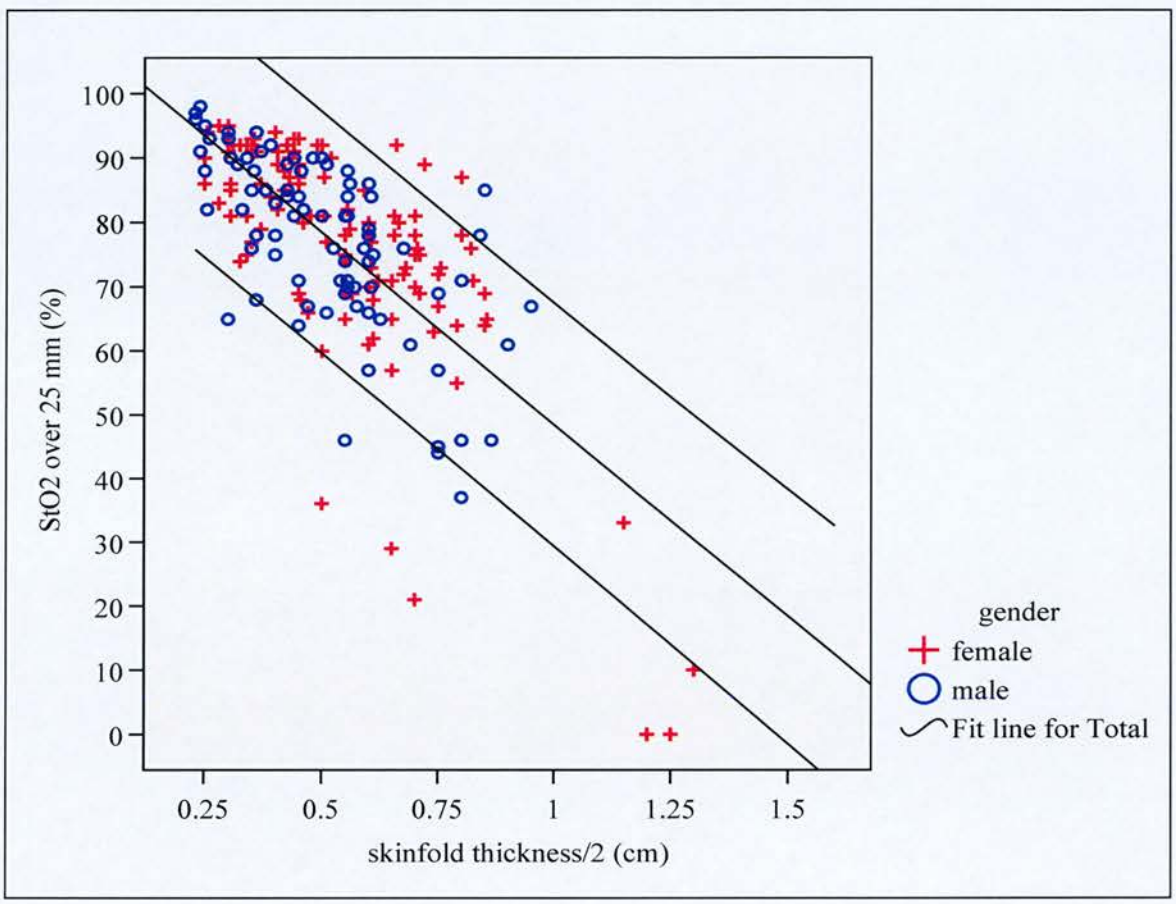

Figure 62 StO_2 over 25 mm (%) plotted against skinfold thickness (cm) divided by two measured at 5 cm and 10cm distal from the tibial tuberosity. Correlation coeffificient = - 0.69, p <0.01. Equation for linear model: $StO_2 = a + b*skinfold\ thickness/2$, where a and b are constants.

To increase the accuracy of the StO_2 measurement, predicted by InSpectra™, without a control element such as the contralateral normal limb, the skin to fascia distance (or AT) must be known, either by ultrasound or skinfold thickness/2. This would allow a correction for the adipose thickness of the measured StO_2 value. This calibration of the StO_2 value could extend the ability of the InSpectra™ to produce quantitative measurements rather than measurements that are compared to a normal limb or that are observed with respect to time.

4.4 Results - Study 2

Twenty-six volunteers were recruited for the second volunteer study, 13 male and 13 female. The only significant difference in baseline parameters between the sexes were height and weight (Table 34). There was a five-year difference in mean age between the male and female subjects, but this was not significant with the small numbers involved. This study, like the first volunteer study did not select volunteers at random and subjects were selected from within the orthopaedic department.

A measurement of AT, StO_2 at 12 mm, 25 mm and 35 mm and total haemoglobin in the 25 mm light pathway was made at the four sites over the anterior compartment of the right leg in each subject as described in the methods. The individual means were calculated prior to obtaining the group mean values (Table 35).

	All		Male		Female		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Significance**
Age (years)	33.8	±13.3	31.1	±12.7	36.6	±13.8	p = 0.4
Height (m)	1.70	±0.1	1.75	±0.07	1.63	±0.09	p <0.01
Weight (kg)	72.8	±15.8	82.8	±11.7	62.9	±13.0	p <0.01
BMI	25.3	±4.8	27.1	±4.0	23.6	±5.0	p <0.05
Systemic oxygen saturation (%)	97.3	±1.4	97.2	±1.5	98.4	±1.1	p = 0.19
diastolic BP (mmHg)	80	±8	82	±7	79	±8	p = 0.45
smoker	31%		38%		23%		p = 0.39

Table 34 Study 2 - Mean (±SD) baseline values for age, height, weight, Body Mass Index (BMI), systemic oxygen saturation (%), diastolic blood pressure, and proportion of smokers for all volunteers, and divided by sex.

	Male		Female		
	Mean	**SD**	**Mean**	**SD**	**Significance**
Mean skin thickness (cm)	0.17	±0.017	0.16	±0.018	$p = 0.07$
Mean skin to fascia distance (cm)	0.47	±0.15	0.68	±0.15	$p < 0.01$
Mean StO_2 at 12 mm (%)	82.4	±16.3	67.1	±16.1	$p < 0.01$
Mean StO_2 at 25 mm (%)	81.4	±15.0	65.9	±5.8	$p < 0.01$
Mean StO_2 at 35 mm (%)	83.6	±10.2	70.7	±7.5	$p < 0.01$
Total haemoglobin in 25 mm light pathway ($g.dl^{-1}$)	14.8	±7.4	8.2	±2.0	$p < 0.01$

Table 35 Mean skin thickness, mean skin to fascia distance (cm), mean StO_2 (%) values over 12 mm, 25 mm and 35 mm and mean total haemoglobin ($g.dl^{-1}$) in the 25 mm light pathway. All demonstrated significant differences between male and females except the skin thickness.

In keeping with the results in volunteer study one, significant differences between the sexes were observed in skin to fascia distance, at all three depths of StO_2 measurement and in total haemoglobin in the 25mm light pathway. The only significant difference in StO_2 between any of the three different NIRS interfaces was detected between the 25 mm and 35 mm interfaces in women ($p < 0.05$, Wilcoxon Signed test). A significant linear correlation between the StO_2 and skin to fascia distance was demonstrated for all three different NIRS interfaces (Figure 63 a, b and c).

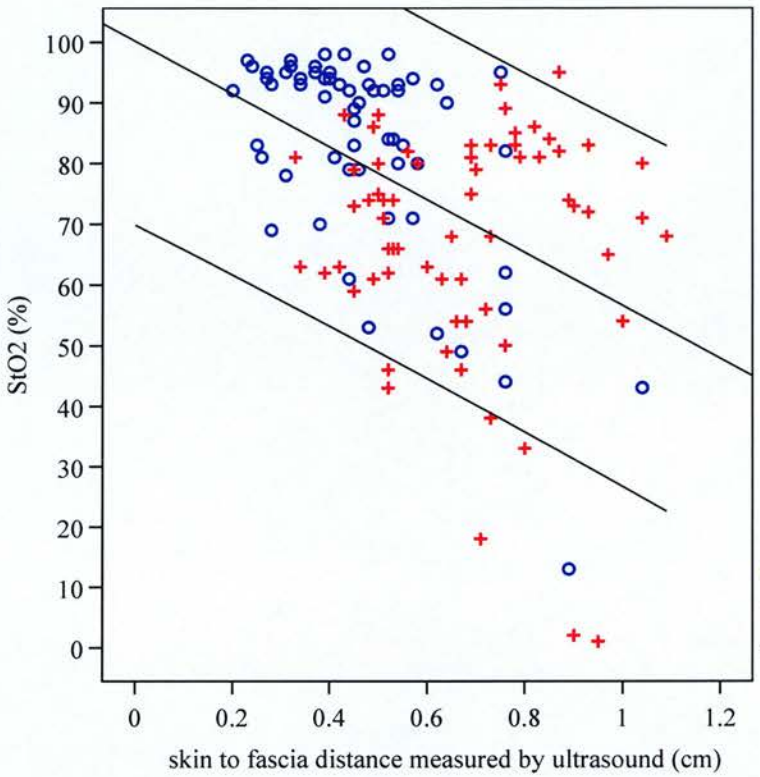

Figure 63a

StO2 (%)

over 12 mm

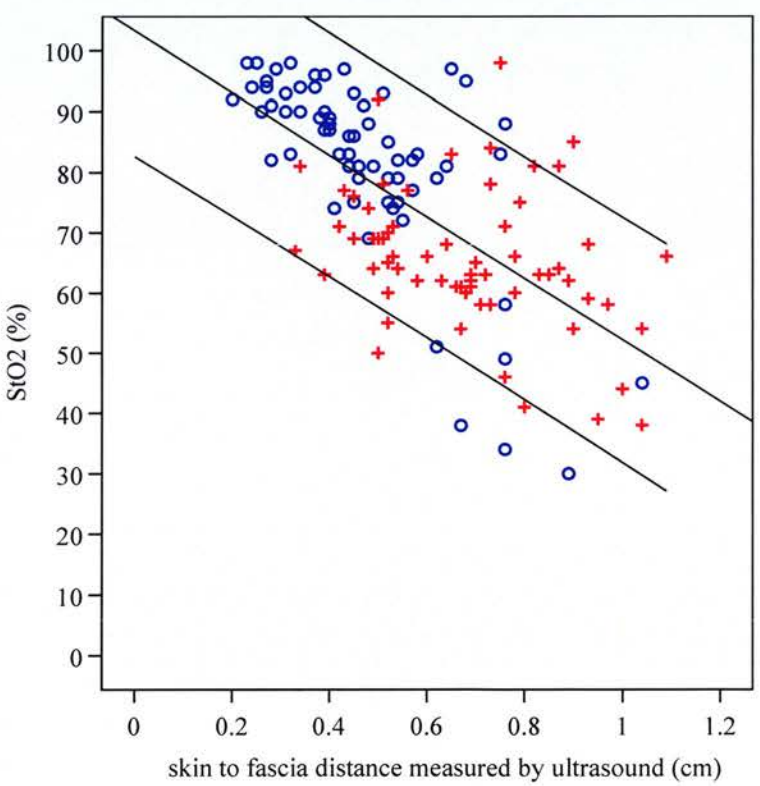

Figure 63b

StO2 (%)

over 25 mm

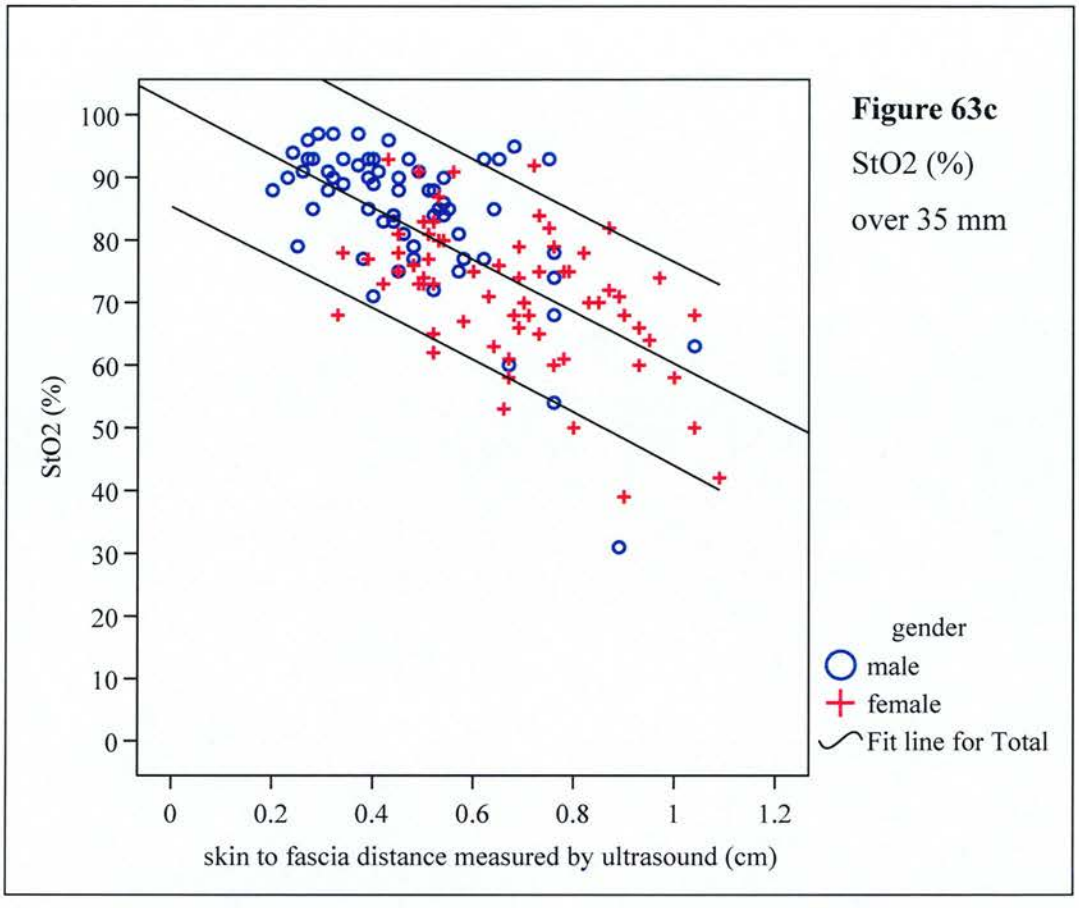

Figure 63a,b,c StO_2 (%) recorded from NIRS interfaces with inter-optode distances of 12mm, 25mm and 35mm plotted against the skin to fascia distance (adipose thickness - AT). Linear correlations and 95% confidence intervals demonstrated. Correlation coefficients are –0.46 for 12 mm, -0.66 for 25 mm and –0.64 for 35 mm ($p < 0.01$ for all)

The facility to record the total amount of haemoglobin in the light pathway was only available for the 25 mm interface. Total haemoglobin is calculated from the sum of the oxygenated and deoxygenated haemoglobin in the light pathway. This additional facility was provided by Hutchinson Technology Inc (HTI), (Hutchinson, Minnesota. USA) as part of one InSpectra^{TM} device. This facility had not been available for any other part of the investigation reported in this thesis.

The total haemoglobin in the tissues measured over the 25 mm light pathway has been shown to differ significantly between the sexes (Table 35). The total haemoglobin correlates significantly with the StO_2 over 25 mm of soft tissue (Figure 64a). This figure clearly illustrates the difference in gender with regard to both StO_2 and total haemoglobin in the light pathway that has been identified in both the clinical and volunteer studies. The relationship is not linear and is best represented by an S-curve model (correlation coefficient = 0.86, $p<0.01$) (Figure 64b).

When the total haemoglobin is plotted with the skin to fascia distance (adipose thickness - AT), a significant correlation was also observed (correlation coefficient = 0.79, $p<0.01$) (Figure 65a). The relationship between total haemoglobin and adipose tissue thickness can be defined by the equation:

$\boldsymbol{skin\ to\ fascia\ distance = a * total\ Hb^{b}}$ where a and b are constants, $a = 1.75$ and $b = -0.52$.

The fall in the total haemoglobin in the 25 mm light pathway that has been observed was associated with an increasing adipose tissue depth, which in turn provides an explanation for the reduction in StO_2 values measured by NIRS with increasing adipose thickness. The data points have been displayed by gender and can be seen to lie at different points on the same curve. This provides an explanation for the apparent differences found between male and female subjects.

Although not as closely correlated with the StO_2 over 25 mm, the StO_2 values recorded over 12 mm and 35 mm also correlated with the total haemoglobin in the 25 mm light pathway. The 'best fit' relationship was also an S-curve model with correlation coefficients = 3.89 and 7.20 for StO_2 values recorded over 12 mm and 35 mm respectively ($p < 0.001$).

The total haemoglobin in the 25 mm light pathway over the leg did not demonstrate a significant correlation with age, height, weight, BMI, systemic O_2 saturation, or blood pressure.

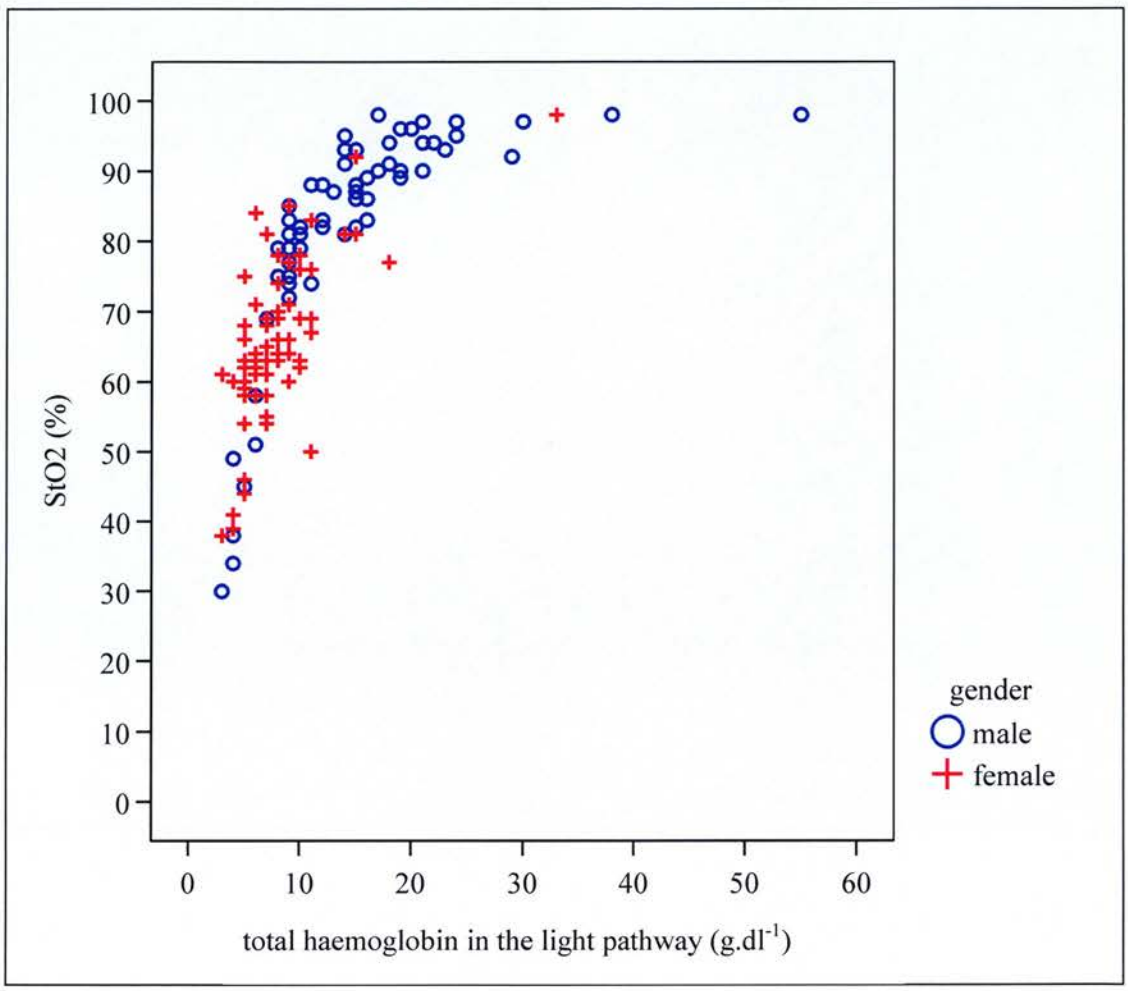

Figure 64a StO_2 (%) over 25 mm by total haemoglobin ($g.dl^{-1}$) in 25 mm light pathway. Data points displayed by gender.

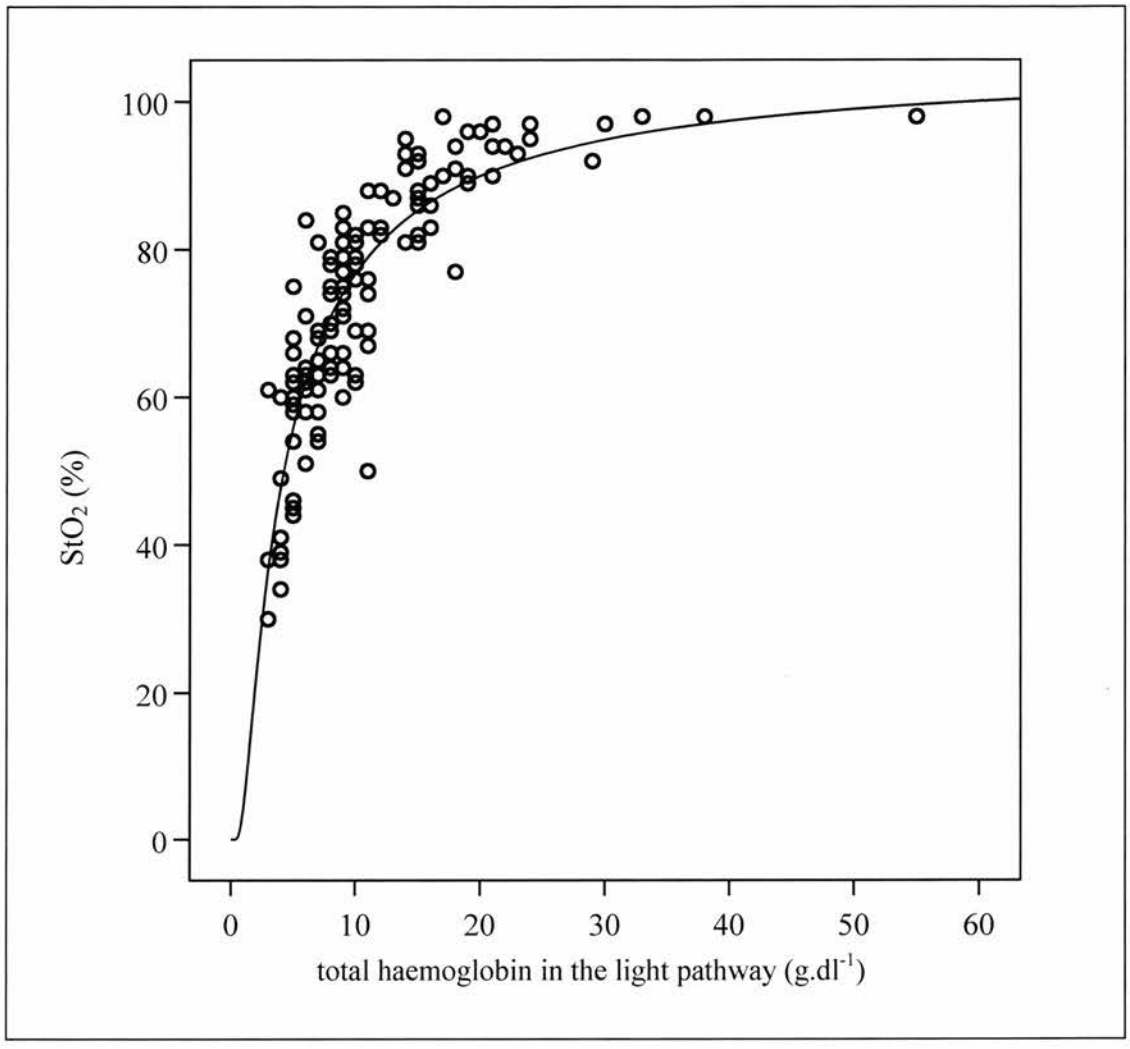

Figure 64b StO_2 (%) over 25 mm by total haemoglobin ($g.dl^{-1}$) in 25 mm light pathway. S-curve model, (correlation coefficient = 0.86, $p<0.01$)
Equation for line: $StO_2 = e^{a + b/total\ haemoglobin}$
where a and b are constants, $a = 4.66$ and $b = -3.18$.

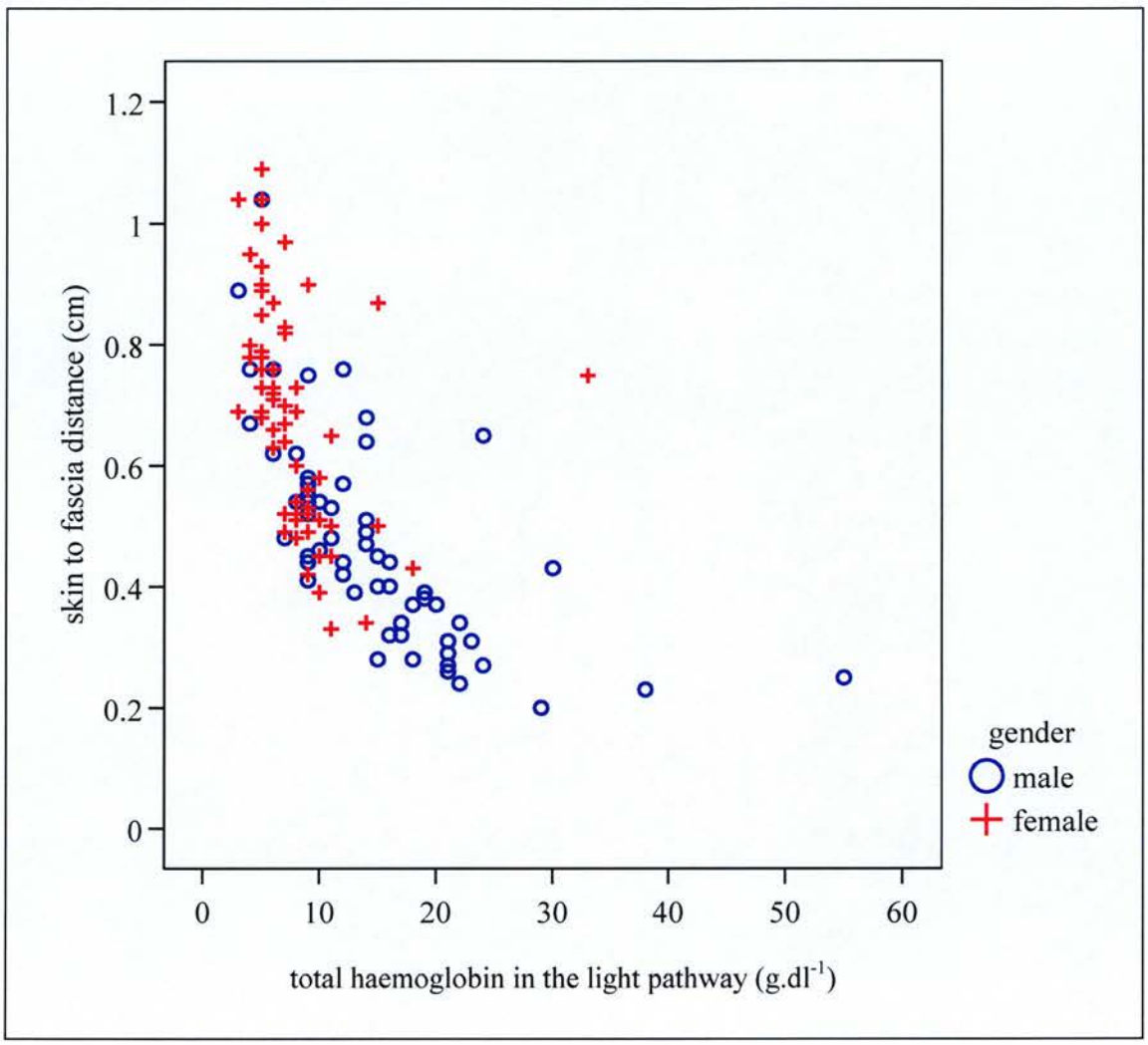

Figure 65a Scatter plot of total haemoglobin ($g.dl^{-1}$) in light pathway (25mm) and skin to fascia distance (cm). Data from male and female subjects shown separately. A decrease in the adipose tissue (skin to fascia distance) corresponds to an increase in the total haemoglobin in the 25 mm light pathway.

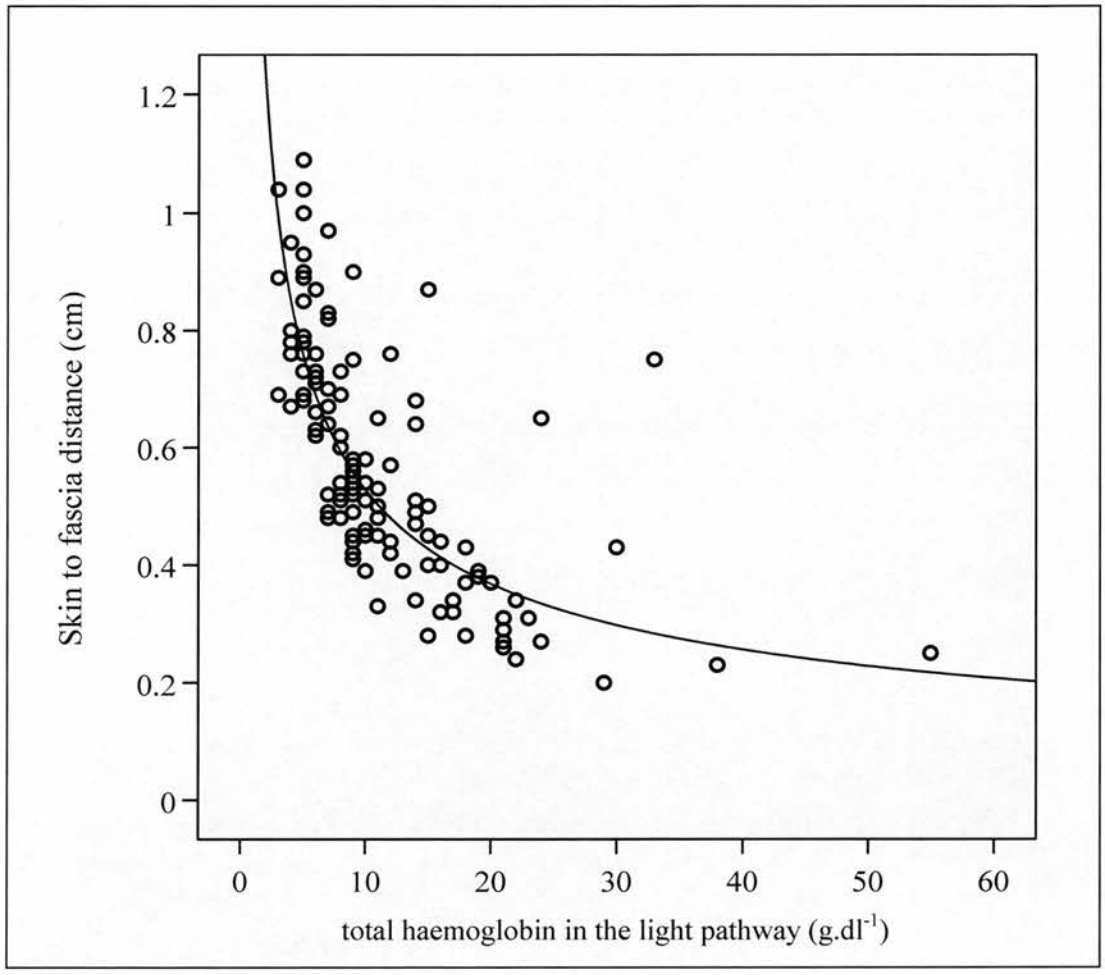

Figure 65b Total haemoglobin ($g.dl^{-1}$) in 25 mm light pathway plotted against skin to fascia distance (cm). Line represents a 'power' model, (correlation coefficient = 0.79, $p<0.01$)

Equation for line: *skin to fascia distance* = a * *total* Hb^b

where a and b are constants, $a = 1.75$ and $b = -0.52$.

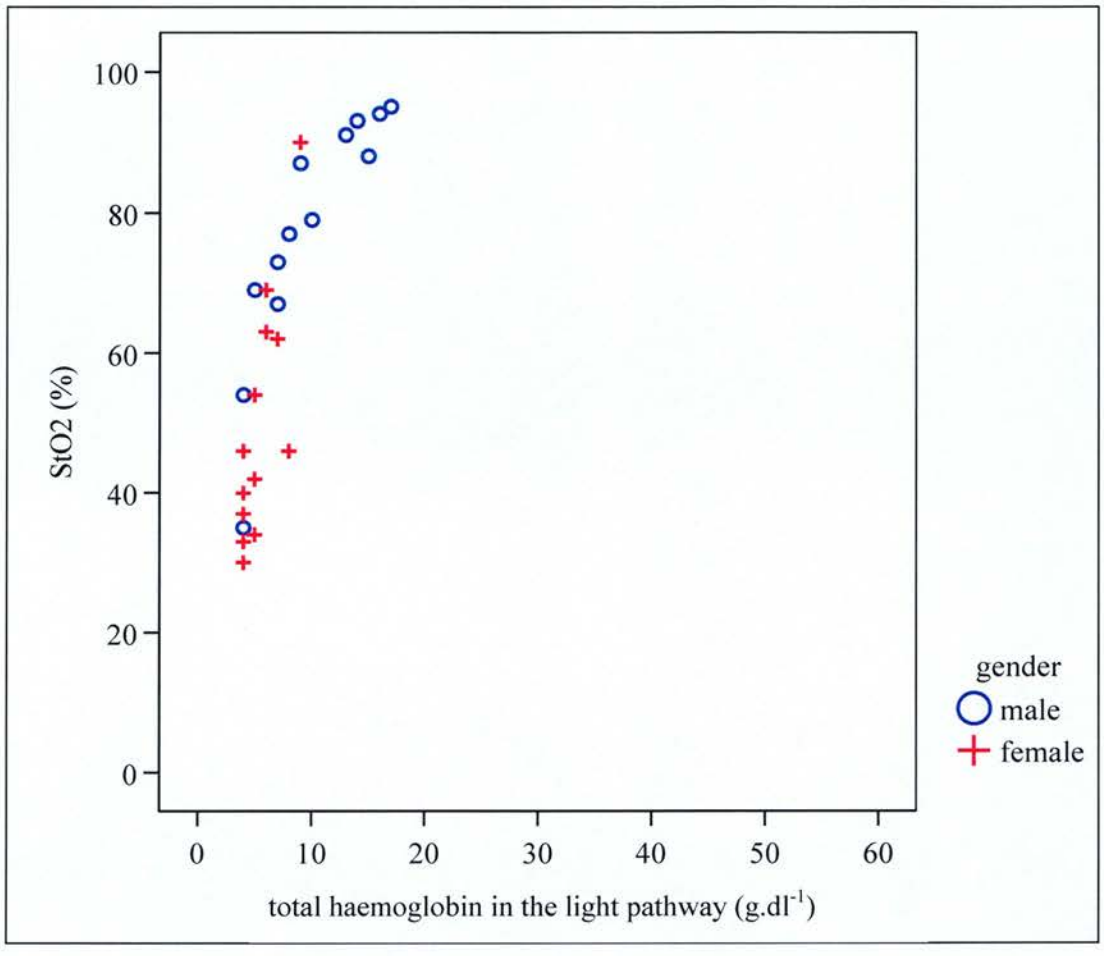

Figure 66 Scatter plot of total haemoglobin ($g.dl^{-1}$) in light pathway (25mm) and StO_2 (cm) over the tibia 10 cm distal from the tibial tuberosity. Data from male and female subjects shown separately.

The relationship between StO_2 over 25 mm and total haemoglobin in the light pathway directly over the tibia at 10 cm distal from the tibial tuberosity again follows a non-linear association similar to that seen over the muscle compartment (Figure 66). Even with small numbers, the mean StO_2 was significantly different between the sexes (StO_2 male 77.1%, SD ± 17.7; female 49.7%, SD ± 17.7, $p < 0.01$). The mean skin to fascia distance over the bone was also significantly different for the two sexes (male 0.60 cm, SD ± 0.24; female 0.83 cm, SD ± 17.7, $p < 0.05$). The data points for the two sexes however, lie along the same curve (Figure 66) and the 'best fit' curve is again an S-curve that has a correlation

coefficient of 0.88 ($p < 0.01$). The similarity of the relationship between StO_2 and the total haemoglobin in the light pathway over bone and muscle indicates that the association is strongly influenced by the depth of adipose tissue due to the low haemoglobin concentration, while relatively unaffected by the contrasting structures of bone and muscle.

4.5 Discussion of the volunteer studies

The volunteer studies have demonstrated that there was a significant gender difference in the mean StO_2 values measured by the InSpectra^{TM} using NIRS (males 81% (± 12), females 61% (± 22)). This difference was suspected in the clinical study and was one of the reasons for the use of the contralateral limb as a control for each individual subject. The use of normal volunteers has suggested that the sex difference in StO_2 value is due to the thickness of the adipose tissue overlying the muscle compartment. In addition, the measurement of the total haemoglobin in the light pathway has correlated with the StO_2 value and adipose thickness. This indicates that the reduced total haemoglobin found in adipose tissue may explain why the StO_2 value falls as the adipose thickness rises. The correlation between the StO_2 and the total haemoglobin implies that the StO_2 value is not merely representative of the ratio between oxygenated and deoxygenated haemoglobin, but is also dependant on the total haemoglobin present in the infrared light pathway.

The observation of a gender difference with regard to NIRS measurements was reported in a study published during the experimental phase of this project (van Beekvelt *et al.*, 2001). Seventy eight volunteers (34 female and 44 male) underwent NIRS measurements over the flexor digitorum superficialis muscle at rest, following venous and arterial occlusion and following hand grip exercise. The interoptode separation was 35mm. The adipose tissue depth was estimated using the skinfold thickness divided by two. Measurements of forearm blood flow were made from the rate of change in total haemoglobin, calculated as the sum of deoxygenated haemoglobin and oxygenated haemoglobin during three venous occlusions. Oxygen consumption was calculated from the rate of decrease of oxygenated haemoglobin during three arterial occlusions. A correlation ($r = -0.71$) was found between oxygen consumption and adipose tissue thickness at rest.

This relationship was significant, but less strong during the periods of exercise. Forearm blood flow weakly correlated with adipose thickness at rest. Oxygen consumption, measured by NIRS was found to be lower in females than males. The oxygen consumption appeared to be twice as high in the ten leanest individuals compared to the ten subjects with the greatest adipose thickness. This study concluded that calculation of blood flow and oxygen consumption is strongly influenced by the depth of the overlying adipose tissue.

The use of ultrasound described in this thesis has provided accurate measurements of the adipose layer thickness (skin to fascia distance). Ultrasonagraphy has been used to determine the adipose layer thickness in previous studies investigating the behaviour of NIRS *in vivo* (Niwayama *et al.*, 2000). The heterogeneity of the tissues through which the light is required to travel has been demonstrated using the ultrasound. Despite the variations in tissue make-up between individuals, the volunteer study of this investigation has provided evidence that there was no significant difference between the sexes in skin thickness of the lower leg to account for the difference in mean StO_2 values. It has also shown that the variability of StO_2 is likely to be more dependant on the adipose tissue thickness rather than the deeper tissue differences such as muscle or bone.

The NIRS instrument that was used in the study by van Beekvelt *et al.* (2001) was believed to have a maximum measurement depth roughly half of the interoptode separation, *i.e.* 18 mm for an interoptode separation of 35 mm. The relationship of measurement depth corresponding to half of the interoptode separation has been previously published (Cui *et al.*, 1991; Matsushita *et al.*, 1998). The InSpectra^{TM} however, is believed to measure from a depth of tissue directly related to the distance between the send and receive optodes (Operator's Manual, Hutchison Technology Incorporated (HTI) Minnesota, USA, 2000). The proportion of the signal that is derived from the muscle, either if the measurement relates to the optode separation or half the optode separation, can be calculated if the

distance from the skin to the fascia is known. A calculation for the percentage of signal derived from muscle for the three interfaces in the second volunteer study has been carried out for the individuals with the greatest and smallest adipose tissue thickness (Table 36).

	Optode separation **12 mm**		Optode separation **25 mm**		Optode separation **35 mm**	
	Depth penetration		Depth penetration		Depth penetration	
	6 mm	12 mm	12.5 mm	25 mm	17.5 mm	35 mm
Smallest adipose thickness (2.6 mm)	56%	78%	82%	89%	85%	93%
Largest adipose thickness (9.1 mm)	0%	24%	27%	64%	48%	74%

Table 36 Percentage of signal derived from muscle for optode separations used in the second volunteer study. Depth penetration given as '$\approx$ *optode separation/2*' or '$\approx$ *total optode separation*'

For individuals with the largest amounts of adipose tissue the 25 mm interoptode separation indicates that at least 60% of the signal is derived from muscle if the depth penetration is equal to the separation. The volunteer studies have demonstrated that these individuals have very low StO_2 values. If the depth penetration of the InSpectra^{TM} were half the interoptode separation (Cui *et al.*, 1991; Matsushita *et al.*, 1998), then only about 20 – 30% of the signal would be derived from the muscle in the individuals with the greatest adipose layers. The predicted percentage of the signal derived from muscle can be calculated using the adipose tissue thickness and compared to the StO_2 for a presumed depth penetration of 12.5 mm and 25 mm for the interface with the 25 mm separation (Figures 67a, 67b). There is a significant correlation between the StO_2 (25 mm separation) and the percentage of signal derived from muscle at both 12.5 mm and 25 mm depth penetration (Spearman's rho $= 0.66$, $p < 0.001$).

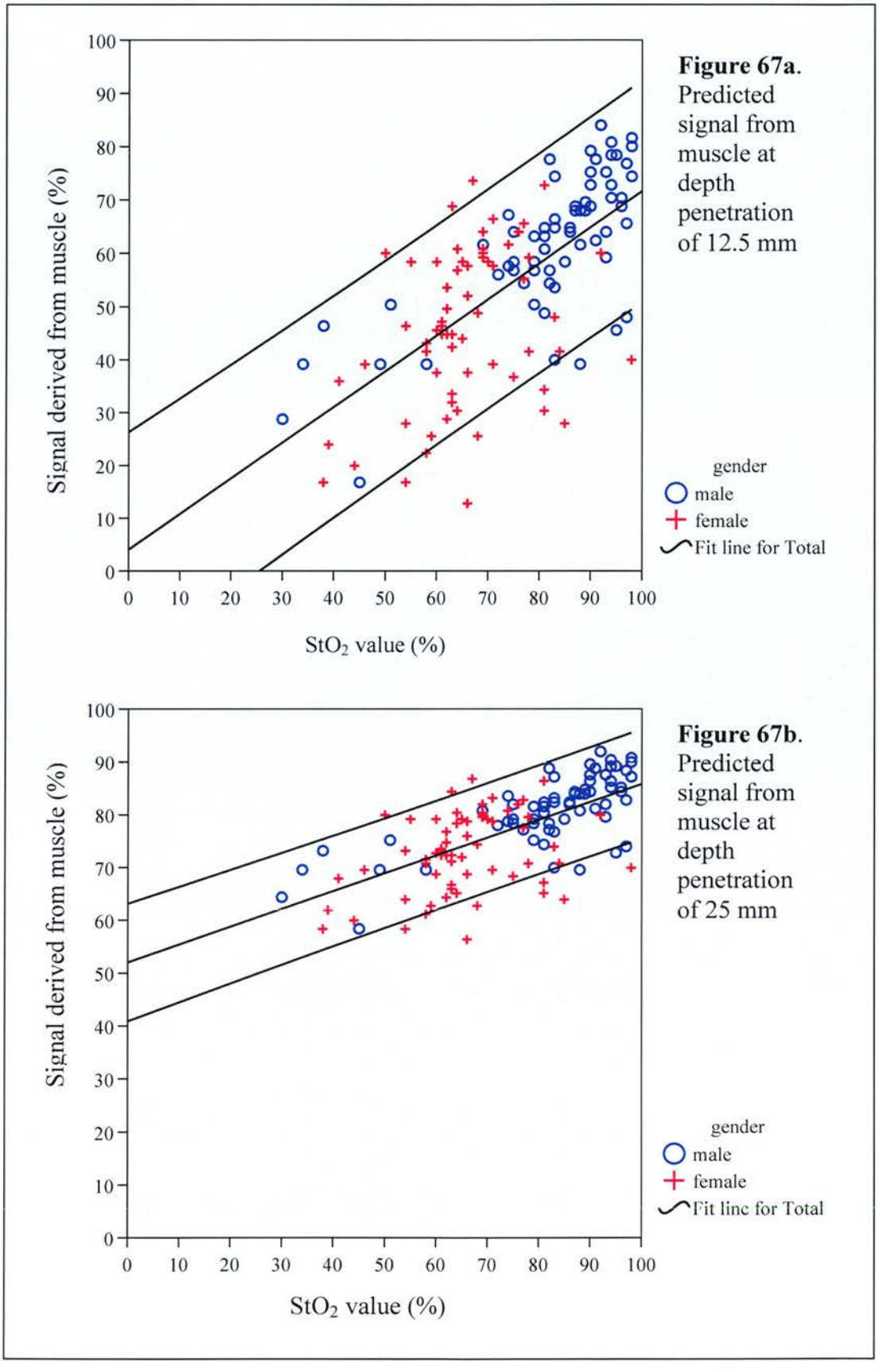

Figure 67a. Predicted signal from muscle at depth penetration of 12.5 mm

Figure 67b. Predicted signal from muscle at depth penetration of 25 mm

Figure 67 Percentage of NIRS signal derived from muscle predicted from penetration depths of 12.5 mm and 25 mm plotted with StO_2 values. Linear models plotted (95% confidence intervals). Data from Volunteer 2 study.

The near-infrared signal of the InSpectra^{TM} is reported to be derived from tissue over a depth of 25 mm from the skin surface (Operator's Manual, Hutchison Technology Incorporated (HTI) Minnesota, USA, 2000). If this is the case, Figure 64b demonstrates that an StO_2 value of 30% is derived from tissue that contains approximately 60% muscle. Figure 67a shows that if the penetration depth of the light is 12.5 mm (interoptode separation distance/2), an StO_2 value of 30% corresponds to approximately 30% of the signal derived from the muscle.

Both of the volunteer studies revealed that female volunteers had greater systemic oxygen saturation as measured by peripheral pulse oximetry. This difference was significant in the first volunteer study with 100 subjects. A gender difference in pulse oximetry values was not observed in previous work with pulse oximetry (Tremper and Barker, 1989). The proportion of female smokers, and the mean age in female subjects was also greater in the first study. The reason for the elevated systemic oxygen saturation is unclear. There were no male outliers with low values to reduce the mean value. The subject with the lowest systemic saturation was a female with a value of 92%. If it had been found that female subjects had a reduced systemic saturation level to begin with, it may not have been possible to establish that the increase in adipose tissue thickness was related to decreased StO_2 measurements.

These volunteer studies and previous work on NIRS and adipose tissue thickness (van Beekvelt *et al.*, 2001) have identified gender differences with regard to the StO_2 recordings. Physiologically males and females differ in respects other than the distribution of adipose tissue. For example, normal ranges of haemoglobin and cardiac output are gender specific. The results from the volunteer studies demonstrate that although the relationship between StO_2, adipose tissue thickness and total haemoglobin in the light pathway is close, there is considerable overlap amongst the two sexes along the same curve

(Figure 64a). This provides the strength to the argument that StO_2 differences are primarily related to adipose thickness rather than gender differences. Although the NIRS measurements are theoretically independent of haemoglobin concentration, it has been demonstrated that StO_2 values produced by InSpectra^{TM} correlated with the total haemoglobin in the light pathway. Some outliers have been observed and in these cases it could be that cardiac output, local blood flow or baseline haemoglobin values could be responsible for some individuals not lying on the curve predicted by the majority. These additional parameters were not investigated in this thesis.

Measurement of the skinfold thickness in the standard sites (biceps, triceps, sub scapula and iliac crest) identified a poor correlation with StO_2 values and adipose thickness on the legs. Anatomical sites distant from the area of interest have been used to establish individual control values for the StO_2 measurement when studying acute compartment syndrome (Giannotti *et al.,* 2000). These 'control StO_2 values' will reflect the adipose tissue thickness at the control site rather than the baseline tissue oxygen saturation of each individual. Anthropomorphic measurements have not identified a useful predictor site of the adipose thickness over the leg.

The propagation of light through biological tissues depends on reflection, scattering and absorption (Jobsis, 1977). Scattering and absorption are dependent on the wavelength of the light. Spectral analysis often assumes tissue homogeneity; however biological tissues are not homogeneous and so have variable scattering and absorption characteristics (Franceschini *et al.,* 1999). The first volunteer study examined the StO_2 values over the tibia. A correlation with the adipose thickness was again seen for both men and women (Figure 59), but the spread of the data points was greatly increased when compared to the measurements made in the same individuals over the muscle compartment at the same level. Measurement over bone adds an extra tissue density change, namely the change from

cortical bone to medullary canal. Geometrically the tibia is triangular in section and NIR light entering 2 cm medially from the subcutaneous border would expect to traverse directly across the bone to the posterior crest, but is likely to coincide with the far cortex at differing distances from the near cortex depending on the angle of incident light and size of the tibia. These factors will increase the degree of tissue heterogeneity when the measurements were made over bone. Obtaining NIRS values over cancellous bone could reduce the degree of tissue heterogeneity and if the adipose thickness was known, may provide information regarding the intra-osseous oxygen saturation.

The second volunteer study has demonstrated that the StO_2 is associated with the total haemoglobin in the light pathway, which in turn relates to the adipose tissue thickness. It has been possible to determine curves in normal volunteers with well oxygenated tissues. To improve the diagnostic effectiveness of the NIRS instrument investigated in this thesis, ranges of StO_2 and total haemoglobin values would need to be established under hypoxic conditions. These conditions can be simulated using venous and arterial occlusion studies. NIRS instruments provide characteristic curves under these conditions. The changes in StO_2 have been recorded using the InSpectra^{TM} over the author's anterior tibial compartment with and without exsanguination during arterial occlusion for three minutes (Figure 68). This preliminary experiment did not have the facility to measure the total haemoglobin in the light pathway. No difference was found between the values with and without exsanguination of the limb. A 'rebound hyperaemic' effect was observed following the deflation of the tourniquet before the values normalised. The changes observed over the bone were less marked than those of the muscle, indicating that oxygen saturation could be maintained for longer in bone during short periods of tourniquet ischaemia. This suggests that a lower rate of metabolic activity may occur within the bone, but no literature has been found to support this.

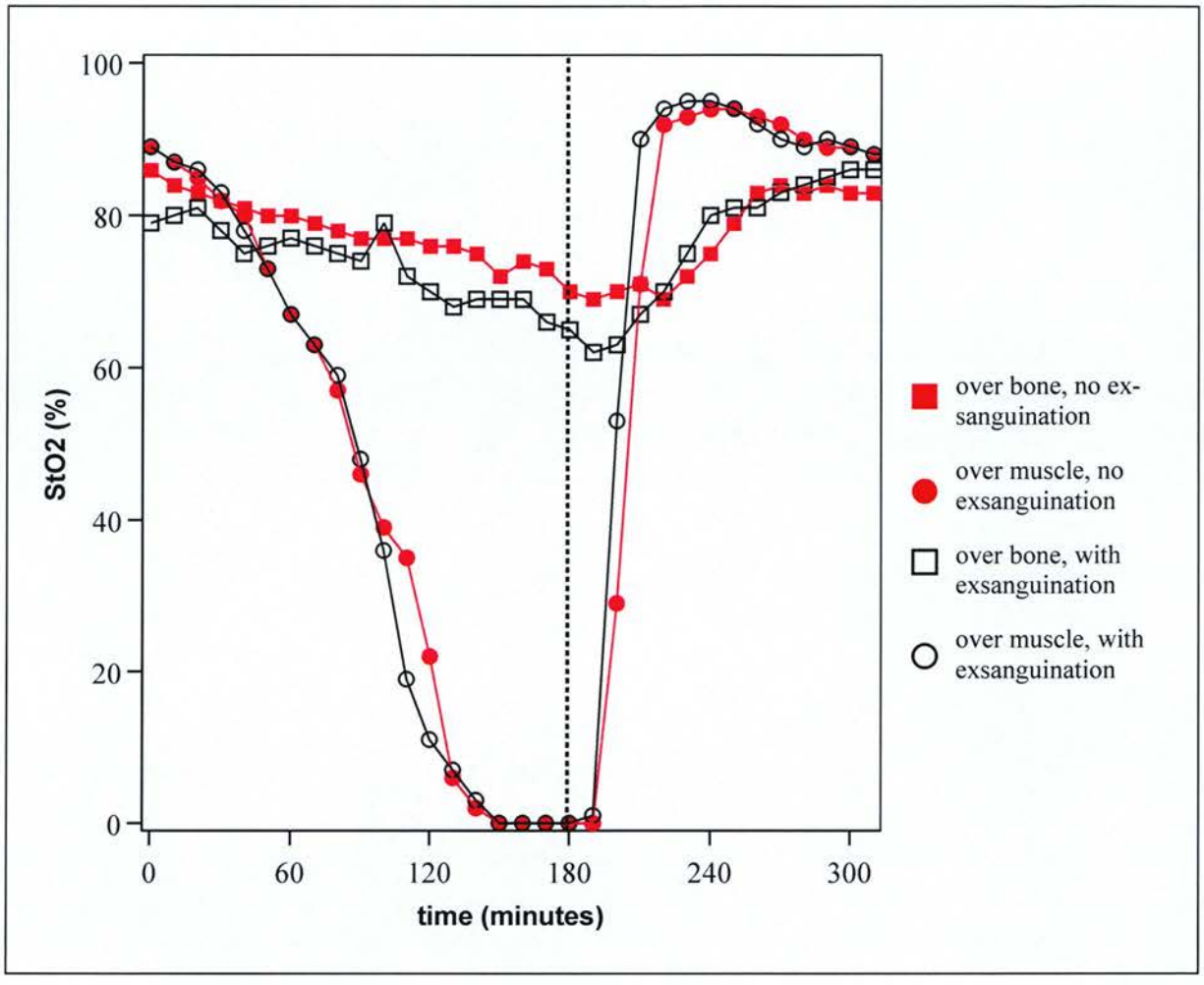

Figure 68 StO_2 (%) measured over the anterior tibial compartment and over the tibia during and following three minutes of thigh tourniquet inflation at 300 mmHg. The X-axis reference line represents the deflation time of the tourniquet (n = 1 volunteer (author))

The recovery of the muscle saturation was rapid which is consistent with the fact that muscle blood flow is five times the blood flow found in cortical bone (McElfresh and Kelly, 1974). Tibial (bone) and tibialis anterior (muscle) perfusion have been investigated using NIRS with a human volunteer model and three minutes of arterial occlusion (Binzoni *et al.*, 2003). It has been demonstrated that with increasing age the rebound hyperaemia decreases and a 'perfusion index' has been calculated corresponding to the gradient of the re-saturation slope. The perfusion index is higher for muscle compared to bone and perfusion

decreases after the age of 30 years. This study did not comment on baseline differences between subjects.

4.6 Conclusion of the volunteer studies

In these volunteer studies it has been shown that the total haemoglobin in the light pathway is proportional to the StO_2 and adipose tissue thickness. This indicates that the total haemoglobin in the light pathway has a significant influence on the StO_2. It has been demonstrated that the resting StO_2 value in a normal subject is related to the adipose tissue thickness. If the StO_2 value is to be useful as a quantitative measurement then the adipose tissue thickness must be taken into account.

The volunteer studies have investigated the effect of the adipose thickness on the StO_2 value in healthy volunteers at rest. It has been shown that the baselines in healthy subjects vary and initial experimental and published work demonstrate clear changes to StO_2 in model hypoxic conditions. The interpretation of the StO_2 value provided by the InSpectra^{TM} for use in clinical scenarios could be assisted by the combined study of the relationship between StO_2, adipose tissue thickness and total haemoglobin in the light pathway during model hypoxic conditions in human volunteers.

5. DISCUSSION

5.1 Strengths of the Study

- The potential of ACS as an application for NIRS clearly identified. The literature review had determined that near-infrared spectroscopy already had clinical applications and therefore to extend its scope to the diagnosis of compartment syndrome was a strong possibility. The study of published work demonstrated a range of perfusion and compartment pressure values that are used to determine the threshold for compartment decompression. In addition, review of clinical practice shows that uniform agreement has not been established as to the relative importance of clinical findings and compartment pressure values for the monitoring of patients with limb injuries (Williams *et al.*, 1998). The application of a non-invasive device has the potential advantage that it could be used by a range of staff members, is painless, does not require an anaesthetic or risk the introduction of infection. The requirement for a new diagnostic tool and a potential device suitable for this role was clearly identified before this study was commenced.

The finding of reduced soft tissue oxygenation in an animal model of acute compartment syndrome (Garr *et al.,* 1999) provided the basis for the progression to a clinical trial of near-infrared spectroscopy for the diagnosis of acute compartment syndrome. The literature review suggested that there was only one previous clinical study, but this only included nine patients (Giannotti *et al.,* 2000). The preliminary animal work for the instrument investigated in this thesis (InSpectra^{TM}) had been completed and the need for a full clinical trial had been identified. A weakness of the study by Giannotti *et al.*(2000), raised in their discussion, was that NIRS had only demonstrated changes in tissue oxygenation in patients who already had a clinical diagnosis of an acute compartment syndrome.

- Study carried out alongside routine compartment pressure monitoring. The clinical trial in this study was completed in a centre that carried out routine continuous compartment pressure monitoring for all patients at risk of an acute compartment syndrome. At this hospital it had been shown that compartment pressure monitoring allowed the detection of an acute compartment syndrome 16 hours earlier than the clinical diagnosis (McQueen and Court-Brown, 1996). This allowed the early detection of an evolving acute compartment syndrome to be compared between non-invasive NIRS and using routine pressure monitoring. This was in contrast to a study where patients had been selected for monitoring who already had clinical signs of an acute compartment syndrome.

- Dedicated orthopaedic trauma unit. The clinical study was carried out in a tertiary referral centre with a dedicated orthopaedic trauma unit with a high turnover that allowed the recruitment of a large number of patients over a short period of time. The hourly recording of compartment pressures by the nursing staff was routine. This allowed the addition of the extra monitor with only minimal instruction, which ensured regular and complete documentation of measurements.

- Statistical significance and clinically important results. The clinical study was able to demonstrate significant correlations between the StO_2 and the compartment pressures. The gradient of the correlations, however, was considerably lower than that which had been expected from the animal results. The animal work had shown that the development of an acute compartment syndrome was associated with a fall of 40% in the StO_2 (Garr *et al.*, 1999). Although statistically significant correlations were observed, clinically important differences were difficult to identify due to the size of the interpatient variability of NIRS recordings.

- Uninjured limb as an individual control. As NIRS spectroscopy is a non-invasive device, it was possible to use the uninjured limb as an individual control for the calculation

of the StO_2 difference. The uninjured limb, however may not be entirely 'normal' in the presence of contralateral trauma due to the existence of reduced blood flow on the un-injured side. This is known as the 'steal phenomenon' (Nutton *et al.,* 1984). Demonstration of an StO_2 difference between the limbs in non-fasciotomy cases may be in part due to the reduced flow in the uninjured side as well as the increase in flow on the injured side. In an acute compartment syndrome leg, the oxygenation to the injured side will be reduced, but it is not known if in these cases whether the steal phenomenon may be larger which could in turn reduce the observed size of the StO_2 difference. Measurements of the StO_2 on the uninjured limbs before and after the fasciotomy of the contralateral side demonstrated a rise from 78 ± 25% to 87 ± 5% in the anterior compartment, 83 ± 14% to 87 ± 5% in the posterior and 78 ± 29% to 90 ± 1% in the lateral compartment (Giannotti *et al.,* 2000). This effect in the uninjured leg seen before and after fasciotomy may represent a reduction in the steal effect due to decompression and treatment of the acute compartment syndrome on the injured leg.

- NIRS recording at multiple sites. The application of the NIRS interface at sites other than the site used in the clinical study (10 cm distal and 2 cm lateral from the tibial tuberosity) demonstrated areas where there was great variation in the StO_2 value. As well as a fall in the StO_2 over the length of the lower leg on the uninjured side, variations over the anterior compartment of the injured leg that did not match the uninjured side were observed. These variations on an injured limb and the observation of darkened blood within the adipose tissue layers seen at fasciotomies provided an indication that additional investigation into the effect of haematoma on NIRS was required. Published animal and volunteer studies have all been carried out on non-traumatised tissue.

- Investigation of potential sources of error. This thesis has allowed the investigation of an instrument with regard to a clinical application where two potential influences on the

NIRS measurements were identified, namely haematoma and gender difference. Carrying out these studies sequentially has allowed the same investigational device to be used in all parts of the investigation, which therefore eliminates the possibility of subtle differences in NIRS technology between devices constructed at different times or by different manufacturers.

- Validation of the porcine model. The animal study was designed to replicate the previously published porcine model (Arbabi *et al.*,1999). This demonstrated that the results could be reproduced at another site by a different investigator. This provides greater validity to the model and as a consequence the observation of an effect on the NIRS recordings with the addition of the haematoma is not therefore due to a change in animal species, site or investigator.

- Confirmation of StO_2 value by invasive gas monitoring. A weakness of the animal study published by Arbabi *et al.* (1999) was that changes in the StO_2 could have been due to measurements made directly from the infusion rather than from the muscle. As a result, the animal study described in this thesis included an invasive monitor for pO_2, pCO_2 and pH. The StO_2 changes that were seen were paralleled by the changes recorded on the invasive monitor. The invasive monitor was able to demonstrate that in the presence of a sub-cutaneous haematoma the oxygenation in the compartment was reduced due to the increasing pressure even though the StO_2 values remained elevated.

- Catheter positions confirmed by ultrasound. The inclusion of the ultrasound scanner for use in this study had a number of advantages. It allowed visualisation of the catheter tip of the invasive pressure monitor to confirm the location with regard to the level fracture. This ensured location of the catheter tip at the site of maximal pressure (Heckman *et al.*, 1994) and thus avoided the need for multiple catheters, placed proximally and distally to calculate a mean value. If two catheters are placed and both lie some distance from the

fracture then the mean value will be lower than a single catheter placed at the site of maximal pressure. Ultrasound images were also used in the animal study to confirm the positions of the invasive pressure monitoring catheter, infusion catheter and invasive pO_2, pCO_2 and pH catheter. This process ensured that all the catheters were within the centre of the anterior muscle compartment beneath the NIRS interface.

- Adipose tissue and skin thickness measurements. Ultrasound has demonstrated that the skin thickness was not significantly different between the sexes. This observation strengthens the argument that the adipose tissue thickness is responsible for the gender differences in StO_2. The skin thickness was not examined in the volunteer study of van Beekvelt *et al.* (2001) where skin fold thickness was the only measurement employed to examine the variations in tissue structure.

- Alternative method to standard skinfold thickness. The volunteer study in this thesis demonstrated a strong correlation between the skinfold thickness (divided by two) and the measurement from the skin surface to the fascia obtained by the ultrasound. The skinfold measurement is easy to take in the non-traumatised limb, but this would not have been possible in the patients with forearm or lower limb injuries. The portable ultrasound scanner enabled these tissue measurements to be made on swollen limbs.

- Swelling not increased in ACS patients. The clinical study of NIRS in nine patients with acute compartment syndrome (Giannotti *et al.*, 2000) does not comment on the possible effect of swelling, particularly when using the contralateral limb as a 'control' value for StO_2. A reduced StO_2 value could be caused by the increase in distance between the skin and fascia or the reduced density brought about by oedema. The use of ultrasound recording in this study demonstrated that superficial swelling was not more significant in patients who later went on to require a fasciotomy.

5.2 Weaknesses of the Study

- Inter and intra-patient StO_2 variations and a single output value. Near-infrared spectroscopy is dependant on the change in absorbance pattern of light that is proportional to the relative amounts of oxygenated and de-oxygenated haemoglobin (Jobsis, 1977). Oxygenated and deoxygenated haemoglobin are represented at different wavelengths. Although it is excepted that NIRS technology is unable to distinguish between haemoglobin and myoglobin due to the similarity in wavelengths, the instrument investigated in this study provided only a single output value. In view of the fact that the preliminary animal work had been carried out and the results were promising (Garr *et al,* 1999), the instrument in this study had been refined to a product suitable for marketing. The instrument worked well and was tolerated easily be the patients, but the inter- and intra-patient variations that were revealed in the clinical and then the volunteer study have been difficult to interpret with only a single output value. For an investigation into the possibility of NIRS detecting an acute compartment syndrome, an instrument that provided raw data on the proportions of deoxygenated and oxygenated haemoglobin may have eased the interpretation of the results obtained.

- Upgrading of the near-infrared spectrometer. The use of the 'upgraded' instruments in the second volunteer study provided additional information with regard to the total haemoglobin in the light pathway. If this instrument had been applied to the limbs of patients in the clinical study it may have been able to indicate either blood flow changes in response to the trauma or localised changes in the total haemoglobin could identify the presence of haematoma in the subcutaneous tissues. This upgraded instrument was not available for the animal study. This study has demonstrated that the StO_2 remains elevated in the presence of a haematoma, but a measurement of the total haemoglobin in the presence

of a haematoma in the animal study could have aided the understanding of results in the clinical study.

- Single investigating instrument for clinical study affected patient selection. The clinical study results suggest a high proportion of cases with a diagnosis of an acute compartment syndrome, made by invasive pressure monitoring. The protocol for the clinical study determined that the NIRS monitor was applied to the patient who was most at risk of an acute compartment syndrome (McQueen *et al.,* 2000). The study was not attempting to establish the rate of fasciotomy or ACS within this orthopaedic unit. By selecting for patients with an acute compartment syndrome, the study identified a greater proportion of patients that fell into the fasciotomy group. It was necessary to anticipate the need for subject selection as only one instrument was available and regularly more than one subject with a forearm or lower limb injury was admitted at the same time. By selecting patients most at risk of an acute compartment syndrome, it is possible that the comparison between the fasciotomy and the non-fasciotomy groups essentially becomes a comparison between patients who definitely have an acute compartment syndrome and those who are borderline. Patients who are at low risk, due to the lack of investigational devices, were on occasions not recruited. This study design could have caused a failure to detect a difference between the acute compartment syndrome cases and those without when one is present (type II error).

- Incomplete monitoring may have produced elevated mean compartment pressures. The clinical study protocol required that monitoring should be applied to those most at risk of an ACS and therefore in some patients the monitoring was not completed for the full 24 hour period after surgery as another patient at greater risk was admitted and the monitoring was then re-located. This selection could have influenced the mean values for the post-operative period in the non-fasciotomy subjects. As the compartment pressures fall during

the first 24 hours after surgery, shortening this period would artificially elevated the calculated mean pressure as only the earlier recordings were carried out. This selection of patients most at risk of an acute compartment syndrome could potentially decrease the size of the difference between the fasciotomy and the non-fasciotomy groups and cause a true difference to be missed (type II error). Improvements to the study could have been made by using a greater number of NIRS monitoring devices so that all patients were monitored for the complete post operative period, thereby reducing any potential selection bias.

- High proportion of excluded patients. Although the clinical study aimed to recruit those patients who were 'at risk of developing an acute compartment syndrome', patients with multiple trauma and those with altered consciousness were not recruited. Adolescent patients were selected according to the inclusion criteria but six patients of less than sixteen years were excluded due to their reluctance to take part in the study. These groups are recognised to be at high risk of developing an acute compartment syndrome (Shaw *et al.*, 1994; McQueen *et al.*, 2000). The number of patients that were admitted with injuries at risk of causing an acute compartment syndrome who were not included in the study was high. Sixty-eight patients were not included. Twenty-six patients were not included due to the author being unable to attend or on annual leave. Eight patients were not recruited as there was only one NIRS monitor and there were 11 multiple injured patients. Had it been possible to use additional resources to recruit these patients, use a further monitoring device and to include multiple injured subjects, then the number of exclusions would have been reduced to 23 and a further 45 patients would have been recruited during the study period. This would have included five patients who had a fasciotomy. The increase in numbers could have improved the statistical significance in the clinical results.

- High rate of fasciotomy. The clinical study was carried out in a centre that has previously demonstrated that invasive monitoring in a suspected acute compartment

syndrome led to early decompression and the prevention of the development of sequelae of an acute compartment syndrome (McQueen *et al.,* 1996). The threshold for decompression was a differential pressure or ΔP of less than 30 mmHg. It has been argued that decompression of cases using such a value could lead to the over treatment of an acute compartment syndrome (Janzing and Broos, 2001). The rate of fasciotomy over the study period, taking into account the rate of fasciotomies in the excluded patients, was 18.5%. This figure is higher than previously reported from the same centre, where the fasciotomy rate of 2.6% was found in a prospective study of 116 patients using the same decompression criteria (McQueen and Court-Brown, 1996). It is acknowledged that invasive compartment pressure monitoring heightens the awareness of the possibility of the development of an acute compartment syndrome, and therefore has the potential of leading to over diagnosis if the pressures are not interpreted appropriately. A single value of ΔP of less than 30 mmHg does not mean that a compartment syndrome has developed, but the persistence of this value is associated with increased risk of having an acute compartment syndrome and therefore the values need to be watched closely so that an appropriate and timely surgical intervention can be carried out. The high rate of fasciotomy in this study may indicate that a surgeon following this unit protocol 'to the letter' is carrying out a fasciotomy for relative compartment hypertension. It is known that fasciotomy is associated with scar morbidity (Fitzgerald *et al.,* 2000), but very early decompression is more likely to allow direct wound closure at 48 hours. The high rate of very early fasciotomy is therefore not necessarily unwise, but a high rate of late fasciotomies would cause considerable morbidity due to the requirement for skin graft coverage. With respect to this study, very early decompression, possibly before muscle ischaemia has developed, may have taken place and could explain the equivocal results for the StO_2 value in some of the fasciotomy patients.

- Pre-ischaemia compartment decompression. It is possible that in the clinical study reported in this thesis, the continuous invasive pressure monitoring is able to detect potential acute compartment syndromes very early and perhaps prior to the development of tissue ischaemia. The monitoring of an alcoholic patient with advanced clinical signs of an acute compartment syndrome provides evidence that NIRS does have the ability in humans to detect an acute compartment syndrome in the presence of ischaemia and absence of haematoma. He was not included in the study as pressure measurements had not been carried out. The decompression of compartments prior to the development of ischaemia may be in part why the NIRS in the clinical study was unable to detect an ACS as clearly as that which had been predicted from the animal work (Garr *et al.*, 1999).

- Limitations of comparison between animal model and clinical study. The clinical study had a threshold value for decompression of a ΔP of less than 30 mmHg, whereas the animal study (Garr *et al.*, 1999) found that the development of an acute compartment syndrome occurred with a mean ΔP of 4.1 mmHg. Data from the porcine model by Garr *et al.* (1999) indicates that the animals, before the infusion into the compartments had begun, had a mean ΔP of 28.4 mmHg. The mean starting ΔP in the animal study in this thesis was 28.6 mmHg and the mean ΔP at the development of an acute compartment syndrome was – 42.3 mmHg. The pigs had a low mean diastolic blood pressure (49.8 ± 7. 9 mmHg) and high mean resting compartment pressure (24.2 ± 6.5 mmHg) in this model. The human subjects in the clinical study had a mean diastolic pressure of 74.0 ± 12.7 mmHg. The calculation of the ΔP in the pigs produces a relatively low value indicating a low perfusion pressure to the compartment. This value for the mean resting perfusion pressure in pigs is associated with a mean StO_2 measurement of 72.6 ± 7.6%. The mean resting perfusion pressure in the porcine model is lower than the cut-off for a fasciotomy in the clinical study. This raises two points: firstly, that these differences in values illustrate that direct

extrapolation between animal models and clinical studies should be made with reservation and secondly, that the decompression of patients at a threshold ΔP of less than 30 mmHg may be associated with a normal StO_2 and it may only be at lower values of ΔP that StO_2 changes are seen.

- StO_2 values for ΔP measurements below 30 mmHg. During the clinical study some patients had ΔP values recorded below the threshold of 30 mmHg during the short periods that they were waiting for fasciotomies. Figure 68 illustrates the relationship between the StO_2 difference (%) and the ΔP (mmHg) at values of ΔP below the 30 mmHg threshold. The ΔP values have been grouped into bands of 10 mmHg. Although there is considerable overlap of the 95% confidence intervals due to the spread of values, the trend is for a rise in the StO_2 difference as the ΔP value increases. The reduction in StO_2 in the injured limb predominantly occurred at lower ΔP values than 30 mmHg. The number of data points below a ΔP of 30 mmHg was only 151 compared to 1089 between 30 mmHg and 50 mmHg as the majority of these patients went on to have a fasciotomy due to a ΔP of less than 30 mmHg.

- Absence of intra-operative and post-operative StO_2 measurements. Soft tissue oxygenation values were recorded in the clinical study in acute compartment syndrome subjects prior to the fasciotomy only. StO_2 measurements were not made during and/or after the fasciotomies. The NIRS monitor investigated in this study did not have a sterile attachment at the patient interface as the monitor had been designed for skin surface only. It could have been possible to apply the interface during the fasciotomy using a sterile bag, but direct application of the interface on the muscle would have altered the value by means of removing the soft tissues layers from the light pathway. The interface could have been applied to the side of the fasciotomy, but this would then be recording from a different site and as this study has demonstrated, NIRS recordings vary according to the position on the

limb and with the removal of the superficial adipose layers. No preliminary work had been carried out using a direct application of the instrument onto muscle and therefore pre- and post-fasciotomy StO_2 values and direct application of the instrument to ischaemic muscle was included as part of the animal study.

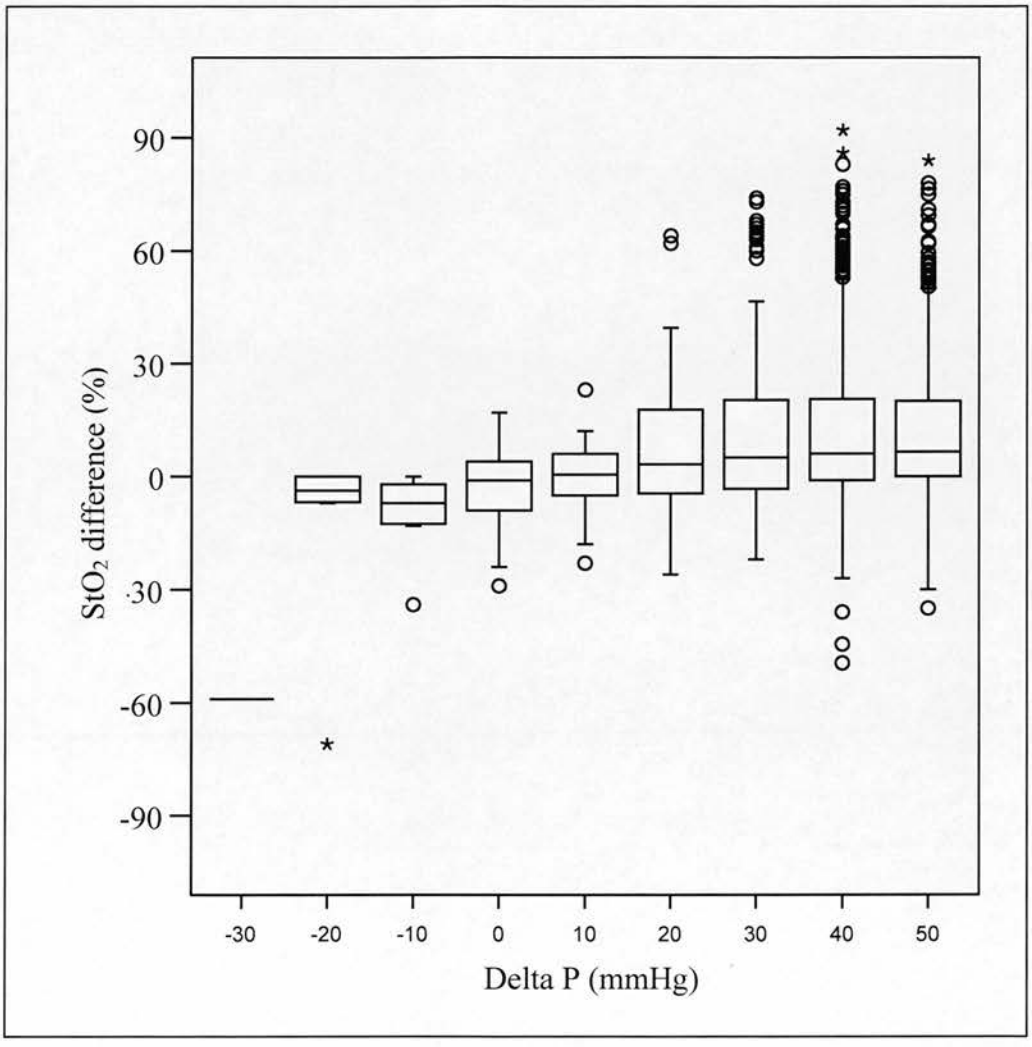

Figure 69 Boxplots of ΔP (mmHg) and StO_2 from the clinical study. The ΔP values have been grouped in bands of 10 mmHg. The threshold for fasciotomy was a ΔP of less than 30 mmHg. Between ΔP 30 mmHg and 50mm Hg there were 1089 data points, below 30 mmHg there were 151 data points. Transverse bars represent mean values and vertical bars represent 95% confidence intervals.

- Low rate and short duration of clinical study follow up. The conclusions drawn from the clinical study with regard to the correlation of StO_2 to compartment pressure were made independently of the follow up of patients. The clinical study as a whole however is weakened by the fact that there was a low rate of follow up of patients. The population from which the study was taken, in the nature of trauma, contains a large proportion of young adult men, a significant proportion of whom were visiting the city and therefore did not return for follow up. The follow up period was also short (mean time 5.6 months). This study was designed to investigate the ability of an instrument to diagnose an acute compartment syndrome. The study was not looking for long-term outcome following a new treatment or threshold for decompression and therefore examination within six months following the injury would identify evidence of any missed compartment syndromes or delayed fasciotomies. It was possible to examine patients for missed compartment syndromes (*i.e.* false negatives) but it is not possible to determine the proportion of false positive acute compartment syndrome diagnoses. Specific outcome scores for limbs following fasciotomies are not available. Formal assessment of limb function and muscle group strength was beyond the scope of this project and therefore not carried out.

- Larger numbers needed to reach statistical significance. The differences detected in StO_2 values between the fasciotomy and non-fasciotomy patients was not as great as predicted from the previous animal work (Garr *et al.*, 1999). The clinical study recruited 102 patients. A statistically significant difference was demonstrated with regard to the StO_2 difference with these numbers, but a difference was not detected when the StO_2 was examined without comparison using the uninjured side. It is possible that recruitment of greater numbers may have allowed statistical significance to be reached in a number of areas. There were only 10 patients who had StO_2 monitoring following tibial intra-

medullary nailing. These patients demonstrated a mean StO_2 fall of 6%, which was not statistically significant. The recruitment of patients to the study was formally terminated after discussion with Hutchinson Technology Inc, Hutchinson, USA (Appendix K) due to the unexpected inconsistency of NIRS values in injured limbs.

- No control for systemic changes in porcine model. The animal study in this thesis established that the model of Garr *et al.* (1999) was reproducible and allowed the investigation of the influence of intramuscular haematoma and subcutaneous haematoma on NIRS. In each experiment the contralateral limbs were used as the control side and the experimental design ensured that the only difference between the limbs was the presence of the intramuscular infusion. Each animal also had systemic monitoring via the carotid artery and had arterial blood gases measured. A potential weakness of the experimental design was that there had been no allowance for a control animal without an acute compartment syndrome. It has not been possible therefore, to confirm that changes seen in the arterial blood gases, temperature and potassium levels were due to the prolonged anaesthesia or were as a consequence of the developing acute compartment syndrome. In future work it would be important to confirm the cause for the baseline changes in case these variations are due to the acute compartment syndrome. Hyperkalaemia is known to be associated with both prolonged anaesthesia and also re-perfusion following muscle ischaemia (Gil *et al.*, 2004; Waikakul *et al.*, 1998). Systemic changes in response to a developing acute compartment syndrome could provide an important and useful adjunct for monitoring for an acute compartment syndrome.

- No histological analysis. In the animal study, the use of the invasive monitor for pO_2, pCO_2 and pH confirmed that ischaemic changes were taking place within the muscle compartment, but these changes have not been confirmed by histological analysis. Analysis of muscle biopsy samples would provide additional evidence to confirm that an

ischaemic process has occurred. Immunochemical analysis could also be performed to look for markers of muscle damage.

- Normal variation and sources of error not established before clinical study. An investigation into normal values for a new instrument would ordinarily take place prior to carrying out a clinical study. The Inspectra ^{TM} had been validated against *in vitro* isolated perfused tissue (Operators Manual, Hutchison Technology Inc, Minnesota, USA). Following the promising animal results (Garr *et al.,* 1999) the device was shown to detect a simulated acute compartment syndrome in human volunteers (Gentillelo *et al.,* 2000). Variation in StO_2 readings between the subjects were not reported. This thesis may have been improved had the investigation begun with a full examination of normal variations in the population.

- Randomisation of volunteers. The volunteer study could have been improved by a randomistion in the subject selection. This would have allowed more accurate identification of gender differences in NIRS recordings. The fact that recruitment was made on a non-random basis did not influence the observation of a statistically significant correlation between the StO_2 and adipose thickness that held true for both men and women.

- Normal StO_2 in the presence of reduced blood flow. Near-infrared spectroscopy provides a value for soft tissue oxygenation, StO_2. It must be remembered that this value reflects the oxygen carrying capacity of the blood in the tissue. It does not reflect the blood flow or the total volume of blood in the tissue. A haematoma that has a high oxygen carrying capacity can cause an elevated StO_2 although there is no blood flow. It is with this in mind that the StO_2 value must be interpreted. The animal and clinical studies have demonstrated that StO_2 measurements in traumatised limbs do not reflect those seen in physiologically normal tissues.

5.3. Conclusions

This study has identified a significant correlation between soft tissue oxygenation, measured non-invasively by near-infrared spectroscopy, and compartment pressure. However, as a diagnostic tool for acute compartment syndrome, NIRS has been found to provide measurements that are inconsistent. This will limit the use of NIRS in the diagnosis of acute compartment syndrome until further research has been carried out.

It has been demonstrated that calculating the difference between the injured and uninjured limbs can reduce the inter-patient variability of StO_2 measurements. The value of StO_2 has been shown to decrease as the adipose tissue thickness increases and to rise and remain elevated in the presence of a subcutaneous haematoma. The effect of an injury has been seen to result in a rise in the StO_2 on the injured side.

In volunteer subjects it has been shown that the total haemoglobin in the light pathway is proportional to the StO_2 and adipose tissue thickness. This indicates that the total haemoglobin in the light pathway has a significant influence on the StO_2 value.

This study was the first large study of NIRS in patients at risk of an acute compartment syndrome. Earlier work, in normal tissue, indicated the potential of NIRS for diagnosing an acute compartment syndrome. Interpretation of the StO_2 value in traumatised tissue has been difficult. The inclusion of additional basic parameters that can be measured by NIRS such as total haemoglobin, haematocrit and oxyhaemoglobin in future studies is likely to allow the potential of NIRS in this field to be maximised.

The work contained in this thesis indicates that near-infrared spectroscopy should presently be restricted to qualitative measurements in non-traumatised tissues and quantitative values of StO_2 should only be produced following calibration for adipose tissue thickness.

5.4. Future Investigations

This study into the diagnosis of acute compartment syndrome using near-infrared spectroscopy has highlighted particular areas that require investigation if the full potential of NIRS is to be recognised. It has been demonstrated that the StO_2 value is elevated in the presence of a subcutaneous haematoma. NIRS also has the capacity to determine the total haemoglobin in the light pathway. The difficulty with monitoring over traumatised tissue is establishing when extravasated blood is present that could lead to an inappropriately elevated StO_2 measurement. If the adipose tissue thickness is known, then the normal value for the total haemoglobin could be predicted from graphs produced in normal volunteers. If the total haemoglobin in the pathway is greater than the predicted value then it is likely to be due to the presence of extravasated blood. The interface could then be moved to a site over the compartment where the light pathway haemoglobin is normal before StO_2 measurements are carried out.

The follow up in this study highlighted the need for reproducible evaluation criteria to look for the specific signs of missed or delayed diagnoses of an acute compartment syndrome. These signs include a spectrum of contractures and weaknesses that reflect both the range of initiating injuries and the variety of different muscles in the legs and forearms. The muscle weakness following a fasciotomy may be due to delay or inadequate decompression, whereas it may also be due to fibrosis or the destruction of the compartment as a functional unit. Likewise, it is difficult to determine the origin of joint stiffness. It may be due to immobilisation after the injury or could be secondary to soft tissue contractures as a result of an acute compartment syndrome. A scoring system looking specifically for acute compartment sequaelae may improve the accuracy of future investigations.

The clinical study demonstrated that the StO_2 values decreased longitudinally from proximal to distal in the leg over the anterior compartment. The adipose tissue thicknesses

over the length of the legs were not recorded. It has not been possible therefore, to determine if the fall in the StO_2 is due to the increase in adipose tissue thickness or due to an actual reduction in the tissue oxygen saturation.

In this thesis, an observation has been reported with regard to the difference in the rate of fall and normalisation of bone and muscle StO_2 values after application and release of an arterial tourniquet (Figure 68). By examining this effect over the tibia and tibialis anterior muscles, NIRS has been used to determine a 'post ischaemic reperfusion capability' (Binzoni *et al.*, 2003). It has been demonstrated that the bone reperfusion capability is lower than muscle and decreases in volunteers over the age of 50 years. A potential future investigation could examine any association between the limb reperfusion capability and union after tibial fracture. If such an association was found then NIRS could potentially be a useful tool for the early prediction of a tibial non-union.

The animal model was used to demonstrate the effect of a subcutaneous haematoma on the NIRS recordings. This study has also shown that a centrally placed haematoma within the muscle does not adversely affect the ability of NIRS to detect an acute compartment syndrome. In contrast, any potential effects of direct injury to the muscle over which StO_2 recordings may be taken have not been investigated. Injured limbs may have muscle that has been crushed. This could cause direct injury to the muscle fibres which may result in cellular oedema in addition to extravasation of blood into the muscle tissue. The effect of this muscle crush injury on NIRS is presently unknown.

This study has focused on the use of NIRS to measure tissue oxygen saturation in individuals at rest. NIRS has also been used to assess forearm blood flow in a dynamic experiment using sustained handgrip exercise (van Beevelt, *et al.,* 2001). In addition to the studies reported in this thesis, the Inspectra^{TM} has been applied to the anterior leg to record the StO_2 values during and after 60 seconds of sustained ankle dorsiflexion in a normal

individual (Figure 70). StO_2 over the anterior muscle compartment was seen to fall and recover rapidly, whereas over bone the value was unchanged. Patients with chronic compartment syndrome develop symptoms of anterior leg pain over a short period of sustained and repetitive muscle activity. NIRS could be used to investigate the rate of recovery of StO_2 following a single or repeated periods of sustained ankle dorsiflexion.

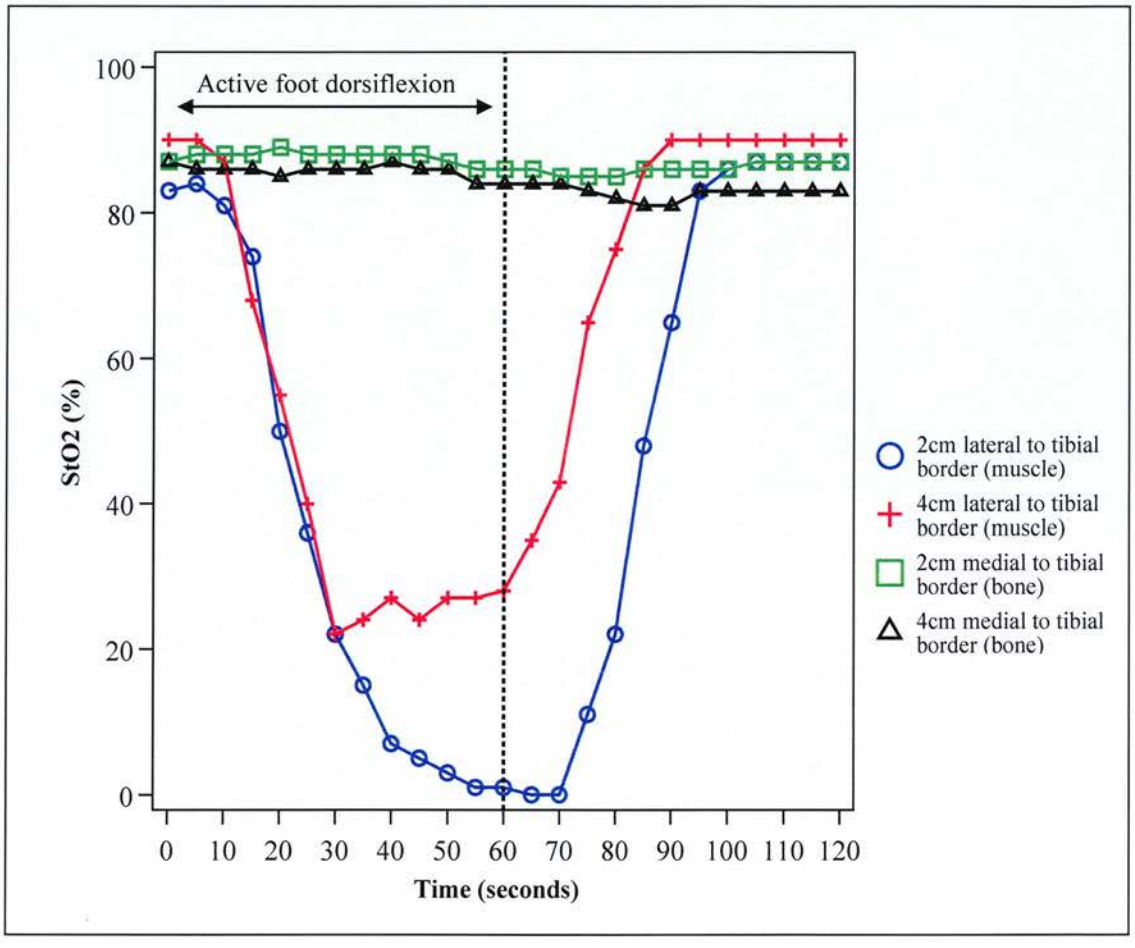

Figure 70 StO2 (%) values using 25 mm interface measured over the anterior compartment of the lower leg during and after 60 seconds of sustained ankle dorsiflexion. Measurements were made equidistant, medial and lateral, from the subcutaneous border of the tibia. To the lateral side measurements were over the anterior compartment, to the medial side the values were taken over bone.

It is possible that the rate and amplitude of recovery of StO_2 may be altered in chronic compartment syndrome patients.

StO_2 changes in the leg have also been observed when a volunteer changes from sitting to standing. The interface was applied over the anterior leg and recordings were made with the individual seated on a bed, with knees fully extended and hips flexed at 45 degrees. The individual was at rest for five minutes before recordings were started. After the first measurement the volunteer then stood unaided for four minutes before returning to the starting position (Figure 71). □

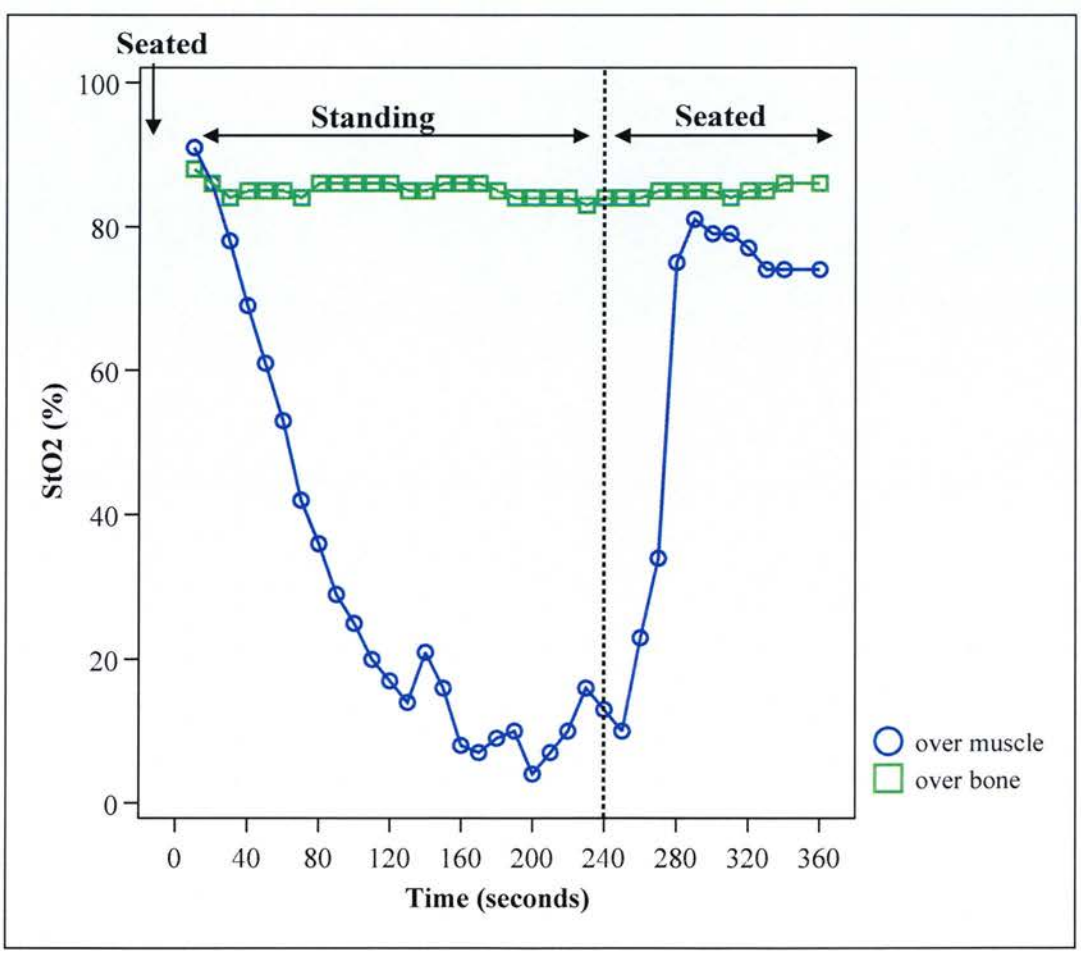

Figure 71 StO2 (%) over 25 mm depth measured at time = 0 in a seated position with legs extended. Subject then stood for 4 minutes (240 seconds - reference line X-axis) followed by returning to the seated position. NIRS measurements taken 10 cm distal from the tibial tuberosity, 2 cm laterally (over muscle) and 2 cm medially (over bone)

The observation of the change in StO_2 during muscle contraction and with position confirmed the necessity that the subjects in this clinical investigation should be both relaxed and in the same seated position for measurements to be made. Further investigation into the contraction and position effects on NIRS in the leg has not been carried out. It is unclear if the drop in StO_2 associated with standing is due to muscle contraction or is due to the effect of venous pooling.

This investigation has highlighted two additional areas of potential study with regard to blood flow in the limbs. Firstly, the observation of muscle discolouration at fasciotomies (Figure 15) indicated that there may be specific areas within the compartments that are relatively under perfused and at greater risk of ischaemic damage. Identification and location of these areas would influence the positioning of saturation monitors in compartment syndrome in the future and would emphasise the need to ensure that attention is paid to specific areas at the time of fasciotomy. Secondly, NIRS used in the uninjured limb in this study and that of Giannotti *et al.* (2000) have provided evidence to confirm the presence of the 'steal effect' (Nutton *et al.,* 1984). The physiology behind this effect is not well understood and requires further study. It is unknown if the size of the effect is proportional to the degree of contralateral ischaemia. The results published by Gianotti *et al.* (2000) suggest that when the contralateral compartment syndrome was decompressed that the StO_2 levels on the uninjured limb increased.

This thesis has demonstrated the sensitivity of NIRS in detecting changes in the soft tissue oxygen saturation. This sensitivity, although being a strength, also allows the technique to be affected by tissue inhomogeneity in normal and traumatised limbs. Considerable further investigation is required before the StO_2 measurement, as a single parameter, can be usefully applied quantitatively in traumatised tissue for the diagnosis of an acute compartment syndrome.

5.5 Dissemination

Published Abstracts

Hope MJ, Hajducka C, McQueen MM

Invasive and Non-invasive Monitoring for Compartment Syndrome

J Bone Joint Surg Br Proceedings. 2003; **85-B**: 9.

Hope MJ, Hajducka C, McQueen MM

Invasive and Non-invasive Monitoring for Acute Compartment Syndrome

J Bone Joint Surg Br Proceedings., 2003; **85-B**: 99.

Hope MJ, Hajducka C, McQueen MM, Simpson H

Non-Invasive Monitoring for Acute Compartment Syndrome.

Journal of Orthopaedic Trauma. 2003; **17(2)**:141-163.

Posters

Hope MJ, McQueen MM, Simpson H

Non-Invasive Acute Compartment Syndrome Monitoring -

The Influence of Haematoma on Near-Infrared Spectroscopy

At: **Scottish Orthopaedic Association Annual Meeting**

Stirling Royal Infirmary, Scotland June 2002.

American Academy of Orthopaedic Surgeons

New Orleans, USA February 2003.

Presentations

Hope MJ, Hajducka C, McQueen MM

Invasive and non-invasive monitoring for acute compartment syndrome.

Presented at: **Compartment Syndrome Update** March 2001

International Symposium Irsee Cloister, Germany

ABC Travelling Fellowship May 2001

Edinburgh Orthopaedic Trauma Unit,

Royal Infirmary of Edinburgh, Scotland

Scottish Orthopaedic Association Annual Meeting

June 2001. Stirling Royal Infirmary, Scotland

British Orthopaedic Research Society

September 2001. Southampton

British Orthopaedic Association

September 2001. Birmingham

LUHNT – 2nd Annual Research Day

March 2002. Western General Hospital, Edinburgh

North of Scotland Orthopaedic Club

April 2002. Dr. Gray's Hospital, Elgin

8th Meeting of the International Society for Fracture Repair

October 9-11, 2002, Toronto, Ontario, Canada.

6. REFERENCES

Anderson AF, Green NE. Residual functional deficit after partial fibulectomy for bone graft. *Clinical Orthopaedics and Related Research* 1991, **267**: 137

Arbabi S, Brundage S, Gentilello LM. Near-infrared spectroscopy: A potential method for continuous, transcutaneous monitoring for compartmental syndrome in the critically injured patients. *Journal of Trauma* 1999; **47**: 829-833

Ashton H. The Effect of Increased Tissue Pressure on Blood Flow. *Clinical Orthopaedics and Related Research* 1975; **113**: 15 - 26

Bardenheuer G. Die Entstetung und Behandlung der ischämischen Muskelkontraktur und Gangrän. Dtsch. Z. F. Chir. 1911; **108**: 44-201

van Beekvelt MCP, Borghuis MS, van Engelen BGM, *et al.* Adipose tissue thickness affects *in vivo* quantitative near-IR spectroscopy in human skeletal muscle. *Clinical Science* 2001; **101**: 21-28

van Beekvelt MCP, van Engelen BGM, Wevers RA, Colier WNJM. Quantitative near-infrared spectroscopy discriminates between mitochondrial myopathies and normal muscle. *Annals of Neurology* 1999; **46**: 667-670

Bernot M, Gupta R, Dobrasz J, *et al.* The effect of antecedent ischaemia on the tolerance of skeletal muscle to increased interstitial pressure. *Journal of Orthopaedic Trauma* 1996; **10**: 555 –559

Binzoni T, Quaresima V, Ferrari M, *et al.* Human calf microvascular compliance measured by near-infrared spectroscopy. *Journal of Applied Physiology* 2000; **88**: 369-372

Binzoni T, Leung T, Hollis V, *et al.* Human tibia bone marrow: Defining a model for the study of haemodynamics as a function of age by near-infrared spectroscopy. *Journal of Physiological Anthropology.* 2003; **22**: 211-218

Blick SS, Brumback RJ, Poka A, *et al.* Compartment syndrome in open tibial fractures. *Journal of Bone and Joint Surgery* 1986; **68A**: 1348-1353

Boody AR, Wongworawat MD, Accuracy in the measurement of compartment pressures: a comparison of three commonly used devices. *Journal of Bone and Joint Surgery* 2005; **87A**: 2415-2422

Boushel R, Piantadosi CA. Near-infrared spectroscopy for monitoring muscle oxygenation. *Acta Physiologica Scandinavica* 2000; **168**: 615-622

Bradley EL. The anterior compartment syndrome. *Surgery, Gynaecology and Obstetrics* 1973; **136**: 289-297

Brodbelt DC, Taylor PM. Delayed onset malignant hyperthermia in two pigs. *Vetinery Record* 1998; **143**: 76-8.

Brun NC, Moen A, Borch K, *et al.* Near-infrared monitoring of cerebral tissue oxygen saturation and blood volume in newborn piglets. *American Journal of Physiology* 1997; **273**: H682-H686

Chance B. Spectrophotometry of the intracellular respiratory pigments. *Science* 1954; **120**: 767-775

Chautens RC, Irmay F, Hoffmeyer P, *et al.* Spontaneous anterior and lateral tibial compartment syndrome in a Type I diabetic patient: Case report. *Journal of Trauma* 1997; **43**: 140-141

Chiverton N, Redden JF. A new technique for delayed primary closure of fasciotomy wounds. *Injury* 2000; **31**: 21-24

Cohen MS, Garfin SR, Hargens AR, Mubarak SJ. Acute compartment syndrome – effect of dermotomy on fascial decompression in the leg. *Journal of Bone and Joint Surgery* 1991; **73B**: 287-290

Court-Brown CM, McQueen MM Compartment syndrome delays tibial union. *Acta Orthopaedica Scandinavica* 1987; **58**: 249-252

Costes F, Barthelemy J-C, Feasson L, *et al.* Comparison of near-infrared spectroscopy and femoral blood gases during steady state exercise in humans. *Journal of Applied Physiology* 1996; **80**: 1345-1350

Cullen DJ, Coyle JP, Teplich R, Long MC. Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. *Critical Care Medicine.* 1989; **17**: 118-21

Cui W, Kumar C, Chance B. Experimental study of migration depth for the photons measured at the sample surface. I. Time resolved spectroscopy and imaging. *Proceedings of the Inernational Society for Opical Engineering* 1991; **1431**: 180-191

De Blasi RA, Ferrari M, Natali A, *et al.* Noninvasive measurement of forearm blood flow and oxygen consumption by near-infrared spectroscopy. *Journal of Applied Physiology* 1994; **76**: 1388-1393

Deply DT, Cope M, van der Zee P, *et al.* Estimation of optical path-length through tissue from direct time of flight measurement. *Phys. Med. Biol.* 1988; **33**:1433-1442

Dickson KF, Sullivan MJ, Steinberg B, *et al.* Non-invasive measurement of compartment syndrome. *Orthopaedics* 2003; **26**: 1215-8

Dudgeon LS. Volkmann's Contracture. *Lancet* 1902; **1**: 8-84

Durnin JVGA, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *British Journal of Nutrition* 1974; **32**: 77-96

Finkelstein JA, Hunter GA, Richard WH. Lower limb compartment syndrome: Course after delayed fasciotomy. *Injury* 1996; **40**: 342-344

Fitzgerald AM, Gaston P, Wilson Y, Quaba A, McQueen MM. Long-term sequelae of fasciotomy wounds. *British Journal of Plastic Surgery* 2000; **53**: 690-693

Flenly DC. Another non-logarithmic acid-base diagram? *Lancet* 1971; **1**: 961

Foisie PS. Volkmann's Ischaemic Contracture. *New England Journal of Medicine* 1942; **226**: 671-9

Franceschini MA, Gratton E, Hueber D, Fantini S. Near-infrared absorption and scattering of tissue *in vivo. Proceedings of the International Society of Optical Engineering* 1999; **3597**: 526-531

Edwards AD, Richardson C, Van Der Zee P, *et al.* Measurement of haemoglobin flow and blood flow by near-infrared spectroscopy. *Journal of Applied Physiology* 1993; **75**: 1884-1889

Ellis H. Disabilities after tibial shaft fractures. *Journal of Bone and Joint Surgery* 1958; **40B**: 190-197

Garr JL, Gentilello LM, Cole PA, *et al.* Monitoring for compartmental syndrome using near-infrared spectroscopy: a non-invasive, continuous, transcutaneous monitoring technique. *Journal of Trauma* 1999; **46**: 613-618

Gelberman R, Garfin SR, Hergenroeder PT, *et al.* Compartment Syndromes of the Forearm: Diagnosis and Treatment. *Clinical Orthopaedics and Related Research* 1981, **161**: 252-261

Gelberman R, Szabo RM, Minteer-Convery MA, *et al.* Tissue Pressure Threshold for Peripheral Nerve Viability. *Clinical Orthopaedics and Related Research* 1983, **178**: 285-291

Gentilello LM, Sanzone A, Wang Leilei, *et al.* Near-infrared spectroscopy versus compartment pressure for the diagnosis of lower extremity compartmental

syndrome using electromyography-determined measurements of neuromuscular function. *Journal of Trauma* 2001; **51**: 1-9

Giannotti G, Cohn S, Brown M, *et al.* Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. *Journal of Trauma* 2000; **48**: 396-401

Gil AG, Silvan G, Illera M, Illera JC. The effects of anesthesia on the clinical chemistry of New Zealand White rabbits. *Contemporary Topics in Laboratory Animals Science / American Association for Laboratory Animal Science* 2004; **43**:25-9.

Gopinath SP, RobertsonCS, Grossman RG, Chance B. Near-infrared spectroscopic localization of intracranial hematomas. *Journal of Neurosurgery* 1993; **79**: 43-47

Griffiths D L. Volkmann's Ischaemic Contracture. *British Journal of Surgery* 1940; **28**: 239-260

Gustilo RB, Anderson JT. Prevention of Infection in the Treatment of One Thousand and Twenty-five Open Fractures of Long Bones. Retrospective and Prospective analyses. *Journal of Bone and Joint Surgery* 1976; **58A**: 453 – 458

Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures. A new classification of type III open fractures. *Journal of Trauma* 1984; **24**: 742-746

Hampson NB, Piantadosi CA. Near infrared monitoring of human skeletal muscle oxygenation during forearm ischaemia. *Journal of Applied Physiology* 1988; **64**: 2449-2457

Hargens AR, Akeson WH, Schmidt DA, *et al.* Fluid alance within the canine anterolateral compartment and its relationship to compartment syndromes. *Journal of Bone and Joint Surgery* 1978; **60A**: 499-505

Hargens AR, Schmidt DA, Akeson WH, *et al.* Quantitation of Skeletal-Muscle Necrosis in a Model Compartment Syndrome. *Journal of Bone and Joint Surgery* 1981; **63A**: 631- 636

Harman PK, Kron IL, McLachlan HD, Freedlender AE, Nolan SP. Elevated intra-abdominal pressure and renal function. *Annals of Surgery* 1982; **196**: 594-597

Harrington P, Bunola J, Jennings AJ, Bush DJ, Smith RM. Acute compartment syndrome masked by intravenous morphine from a patient-controlled analgesia pump. *Injury* 2000; **31**: 387-389

Heckman MM, Whitesides TE, Grewe SR, *et al.* Histological determination of the ischaemic threshold of muscle in the canine compartment syndrome model. *Journal of Orthopaedic Trauma* 1993; **7**: 199 - 210

Heckman MM, Whitesides TE, Scott RG, Rooks MD. Compartment pressure in association with closed tibial fractures. *Journal of Bone and Joint Surgery* 1994; **76A**: 1285 - 1292

Heppenstall RB, Sapega AA, Chance B, *et al.* The Compartment Syndrome. *Clinical Orthopaedics and Related Research* 1988, **226**: 138-155

Heppenstall RB, Sapega AA, Chance B, *et al.* Compartment syndrome: A quantitative study of high-energy compounds using ^{31}P-magnetic resonance spectroscopy. *Journal of Trauma* 1989; **29**: 1113-1119

Heppenstall RB, Scott R, Chance B, *et al.* A Comparative Study of the Tolerance of Skeletal Muscle to Ischemia. *Journal of Bone and Joint Surgery* 1986; **68A**: 820-827

Heyward VH, Jenkins KA, Cook KL, *et al.* Validity of single-site and multiple site models of estimating body composition of women using near-infrared interactance. *American journal of Human Biology* 1992; **4**: 579-93

Hildebrand O. Die lehre von den ischemische muskellahmungen und kontrakturen. Samml. Klin. Vortrage. 1906; **122** 437

Hoffman WE, Charbel FT, Edelman G. Brain tissue oxygen, carbon dioxide, and pH in neurosurgical patients at risk for ischaemia. *Anesthesia and Analgesia* 1996; **82**: 582-586

Holden CEA. Compartmental Syndromes Following Trauma. *Clinical Orthopaedics and Related Research* 1975; **113**: 95 – 102

Hope MJ, McQueen MM. Acute Compartment Syndrome in the Absence of Fracture. *Journal of Orthopaedic Trauma* 2004; **18**: 220-224

Hosoi Y, Yasuhara H, Shigematsu H, *et al.* A new method for the assessment of venous insufficiency in primary varicose veins using near-infrared spectroscopy. *Journal of Vascular Surgery* 1997; **26**: 53-60

Janzing HMJ, Broos PLO. Routine monitoring of compartment pressure in patients with tibial fractures: beware of over treatment! *Injury* 2001; **32**: 415-421

Jepson PN. Ischaemic Contracture. Experimental study. *Annals of Surgery* 1926; **84**: 785-795

Jöbsis F. Noninvasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977; **198**: 1264-1267

Johnson SB, Weaver FA, Bauer M, et al. Clinical results of decompressive dermatofasciotomy. *American Journal of Surgery* 1992; 1**64**: 286-90

Jones R. Volkmann's Ischaemic Contracture. *British Medical Journal* 1928; **2**: 639-642

Kapoor V, Featherstone J, Jeffery ITA. Acute anterior compartment syndrome of the forearm following lifting a heavy load. *Injury* 2000; **31**: 212

Kappis M. Über Die Ischämische Kontraktur Am Arm. *Jour. Internat. Chir.* 1938; **3**: 149

Karlstrom G, Lonnerholm T, Olerud S. Cavus deformity of the foot after fracture of the tibial shaft. *Journal of Bone and Joint Surgery* 1975; **57A**: 893-900

Kelly RP, Whitesides TE, Transfibular route for fasciotomy of the leg. *Journal of Bone and Joint Surgery* 1967; **49A**: 1022-1023

Kinmonth JB. Factors affecting the diameter of large arteries with particular reference to traumatic spasm. *Surgery* 1949; **26**: 452-471

Kinmonth JB. The physiology and relief of traumatic arterial spasm. *British Medical Journal* 1952; **1**: 59-64

Kirkpatrick PJ, Smielewski P, Czosnyka M, *et al.* Near-infrared spectroscopy use in patients with head injury. *Journal of Neurosurgery* 1995; **83**: 963-970

Kitai T, Tanaka A, Tokuka A, *et al.* Quantitative detection of haemoglobin saturation in the liver with near-infrared spectroscopy. *Hepatology* 1993; **18**: 926-933

Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. *Annals of Surgery* 1984; **199**: 28-30

Kruth CD, Uher B. Cerebral hemoglobin and optical pathlength influence near-infrared spectroscopy measurement of cerebral oxygen saturation. *Anesthesia and Analgesia.* 1997; **84**: 1297-1305

Lin L, Niwayama M, Shiga T, *et al.* Influence of a fat layer on muscle oxygenation measurement using near-IR spectroscopy: quantitative analysis based on two-layered phantom experiments and Monte Carlo simulation. *Frontiers of Medical and Biological Engineering* 2000; **10**: 43 - 58

MacDonald MJ, Tarnopolsky MA, Green HJ, Hughson RL. Comparison of femoral blood gases and muscle near-infrared spectroscopy at the onset of exercise in humans. *Journal of Applied Physiology* 1999; **86**: 687-693

Madsen PL, Skak C, Rasmussen A, Secher NH. Interference of cerebral near-infrared oximetry in patients with icterus. *Anaesthesia and Analgesia* 2000; **90**: 489-493

Mancini DM, Bolinger L, Li H, *et al.* Validation of near-infrared spectroscopy in humans. *Journal of Applied Physiology* 1994; **77**: 2740-2747

Mars M, Hadley GP. Raised compartmental pressure in children: a basis for management. *Injury* 1998; **29**: 183-185

Matava MJ, Whitesides TE, Hutton WC, *et al.* Determination of the compartment pressure threshold of muscle ischaemia in a canine model. *Journal of Orthopaedic Trauma* 1994; **37**: 50-58

Matsen FA. Compartmental Syndrome. A Unified Concept. *Clinical Orthopaedics and Related Research* 1975; **113**: 8-14

Matsen FA, Wyss CR, Krugmuire RB, *et al.* The effects of limb elevation and dependency on local arteriovenous gradient in normal human limbs with particular reference to limbs with increased pressure. *Clinical Orthopaedics and Related Research* 1980; **150**: 187-195

Matsen FA, Winquist RA, Krugmire RB Diagnosis and management of compartmental syndromes. *Journal of Bone and Joint Surgery* 1980; **62A**: 286 – 291

Matsushita K, Homma, S, Okada E. Influence of adipose tissue on muscle oxygenation measurement with NIRS instrument. *Proceedings of the International Society for Optical Engineering* 1998; **3194**: 159-165

McElfresh EC, Kelly PJ. Simultaneous determination of blood flow in cortical bone, marrow and muscle in canine hind leg by femoral artery catheterisation. *Calcified Tissue International* 1974; **14**: 301-307

McKinley BA, Marvin RG, Cocanour CS, Moore FA. Tissue hemoglobin O_2 saturation during resuscitation of traumatic shock monitored using near infrared spectrometry. *Injury* 2000; **48**: 637-642

McQuillan WM, Nolan B. Ischaemia complicating injury. *Journal of Bone and Joint Surgery* 1968; **50B**: 482-492

McQueen MM. Acute compartment syndrome: its effect on bone blood flow and bone union. MD Thesis. *University of Edinburgh.* 1995

McQueen MM, Christie J, Court-Brown CM. Acute compartment syndrome in diaphyseal fractures. *Journal of Bone and Joint Surgery* 1996; **78B**: 95 - 98.

McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. *Journal of Bone and Joint Surgery* 1996; **78B**: 99 - 104.

McQueen MM, Gaston P, Court-Brown CM. ACS - Who is at risk? *Journal of Bone and Joint Surgery* 2000; **82B**: 200-203.

Mortensen WW, Hargens AL, Akeson WH, *et al.* Long-term Myoneural Function After an Induced Compartment Syndrome in the Canine Hindlimb. *Clinical Orthopaedics and Related Research.* 1985; **195**: 289-293

Mubarak SJ, Hargens AL, Akeson WH, *et al.* The wick catheter technique for the measurement of intramuscular pressure. A new research a clinical tool. *Journal of Bone and Joint Surgery* 1976; **58A**: 1016 – 1020

Mubarak SJ, Owen CA. Double-incision fasciotomy of the leg for decompression in compartment syndromes. *Journal of Bone and Joint Surgery* 1977; **58A**: 184–187

Mubarak SJ, Owen CA, Hargens AL, *et al.* Acute compartment Syndromes: Diagnosis and Treatment with the Aid of the Wick Catheter. *Journal of Bone and Joint Surgery* 1978; **60A**: 1091–1095

Mubarak SJ, Carroll NC. Volkmann's contracture in children: aetiology and prevention. *Journal of Bone and Joint Surgery* 1979; **61B**: 285-293

Muellner T, Nikolic A, Schramm W, *et al.* New instrument that uses near-infrared spectroscopy for the monitoring of human muscle oxygenation. *The Journal of Trauma* 1999; **46**: 1082-1084

Müller ME, Nazarian S, Koch P, Schatzker J. In: *The comprehensive classification of fractures of the long bones.* Berlin: Spriger-Verlag, 1990: 158-169

Mullet H, Al-Abed K, Prasad CVR, O'Sullivan M. Outcome of compartment syndrome following intramedullary nailing of tibial diaphyseal fractures. *Injury* 2001; **32**: 411-413

Murphy JB. Myositis. *Journal of the American Medical Association* 1914; **63**: 1249-55

Nario C. Syndrome de Volkmann consécutif à une ligature de l'artére axillaire. *Annales de la Facultard de Médicina de Montevide* 1925; **10**: 560.

Newman RJ. Metabolic effects of tourniquet ischaemia studied by nuclear magnetic resonance spectroscopy. *Journal of Bone and Joint Surgery* 1984; **66B**: 434-440

Newman RJ, Duthie RB, Francis MJO. Nuclear Magnetic Resonance Studies of Fracture Repair. *Clinical Orthopaedics and Related Research* 1985; **198**: 297-303

Nicoll EA. Fractures of the tibial shaft – a survey of 705 cases. *Journal of Bone and Joint Surgery* 1964; **46B**: 373-387

Niwayama M, Lin L, Shao J, Nobuki K, Yamamoto K. Quantitative measurement of muscle haemoglobin oxygenation using near-infrared spectroscopy with correction for the influence of a subcutaneous fat layer. *Review of Scientific Instruments* 2000; **71**: 4571-4575

Nutton RW, Fitzgerald RH, Brown ML, Kelly PJ. Dynamic Radioisotope Bone Imaging as a noninvasive Indicator of Canine Tibial Blood Flow. *Journal Orthopaedic Research* 1984; **2**: 67-74

Oestern H-J, Tscherne H. Pathophysiology and classification of soft tissue injuries associated with fractures. In: Tscherne H, and Gotzen L, eds. *Fractures with Soft Tissue Injuries.* Berlin, Springer-Verlag, 1984: 1-9

Patman RD. Compartmental syndromes in peripheral vascular surgery. *Clinical Orthopaedics and Related Research* 1975; **113**: 103-110

Peterson F. Über Ischämische Muskellähmungen. *Arch. Klin. Chir.* 1888; 37: 675-677

Pollard V, Prough DS, DeMelo AE, *et al.* The influence of carbon dioxide and body position on near-infrared spectroscopic assessment of cerebral hemoglobin oxygen saturation. *Anesthesia and Analgesia* 1996; **82**: 278-287

Pringle J, Roberts C, Kohl M, Lekeux P. Near infrared spectroscopy in large animals: Optical pathlength and influence of hair covering and epidermal pigmentation. *The Veterinary Journal* 1999; **158**: 48-52

Putti V. Considerazioni sulla deformita' di Volkmann. *Jour. Internat. Chir. 1938;* **3**: 189

Puyana JC, Soller BR, Zhang S, Heard SO. Continuous measurement of gut pH with near-infrared spectroscopy during hemorrhagic shock. *Injury* 1999; **46**: 9-15

Robinson CM, O'Donnell J, Will E, Keating JF. Dropped hallux after the intramedullary nailing of tibial fractures. *Journal of Bone and Joint Surgery* 1999; **81B** :481-4.

Rorabeck CH, MacNab I,Waddell J. Anterior Tibial Compartment Syndrome, a clinical and experimental review. *Canadian Journal of Surgery* 1972; **13**: 250

Rorabeck CH, MacNab I. The Pathophysiology of the Anterior Tibial Compartmental Syndrome. *Clinical Orthopaedics and Related Research* 1975; **113**: 52-57

Rorabeck CH, MacNab I. Anterior Tibial-Compartment Syndrome Complicating Fractures of the Shaft of the Tibia. *Journal of Bone and Joint Surgery*. 1976; **58A**: 549-550

Rorabeck CH, Clarke KM. The Pathophysiology of the Anterior Tibial Compartmental Syndrome: An Experimental Investigation. *Journal of Trauma* 1978; **18**: 299-303

Rorabeck CH, Castle GSP, Hardie R, Logan J. Compartmental pressure measurements: an experimental investigation using the slit catheter. *Journal of Trauma* 1981; **21**: 446 – 449

Sanderson RA, Foley RK, McIvor GWD, Kirkaldy-Willis WH. Histological response on Skeletal Muscle to Ischaemia. *Clinical Orthopaedics and Related Research* 1975; **113**: 27-35

Sadasivan KK, Carden DL, Moore MB, Korthius RJ. Neutrophil Mediated Microvascular Injury in Acute, Experimental Compartment Syndrome. *Clinical Orthopaedics and Related Research* 1996; **339**: 206 - 215

Scott DJ, Allen MJ, Bell PR, McShane M, Barnes MR. Does oedema following lower limb revascularisation cause compartment syndromes? *Annals of the Royal College of Surgeons of England.* 1988; **70**: 372-376

Schaser K-D, Vollmar B, Mittlmeier T, *et al.* *In Vivo* Analysis of Microcirculation following Closed Soft-Tissue Injury. *Journal of Orthopaedic Trauma* 1999; **17**: 678-685

Seddon HJ. Volkmann's Ischaemia in the Lower Limb. *Journal of Bone and Joint Surgery* 1966; **48B**: 627-636

Seiler JG, Womack S, De L'Aune WR, *et al.* Intracompartmental pressure measurements in the normal forearm. *Journal of Orthopaedic Trauma* 1993; **7**: 414 – 416

Sisson S. Porcine. In: Sisson S, Grossman JD, Getty R, eds. *The Anatomy of the Domestic Animals.* 5th Ed. Philadelphia: WB Saunders, 1975 :1265-1267

Shaw AD, Sjølin SU, McQueen MM. Crush syndrome following unconsciousness: need for urgent orthopaedic referral. *British Medical Journal* 1994; **309**: 857-859

Schaser K-D, Vollmar B, Menger MD, *et al.* *In vivo* analysis of microcirculation following closed soft-tissue injury. *Journal of Orthopaedic Research* 1999; **17**: 678-685

Seekamp A, Griensven, H Blankenburg, *et al.* Intramuscular partial oxygen tension monitoring in compartment syndrome – an experimental study. *European Journal of Emergency Medicine* 1997; **4**: 185-192

Shakespeare DT, Henderson NJ. Compartmental pressure changes during calcaneal traction in tibial fractures. *Journal of Bone and Joint Surgery* 1982; **64B**: 498-99

Sheridan GW, Matsen FA. An Animal Model of the Compartmental Syndrome. *Clinical Orthopaedics and Related Research* 1975; **113**: 36–42

Sheridan GW, Matsen FA. Fasciotomy in the treatment of acute compartment syndrome. *Journal of Bone and Joint Surgery* 1976; **58A**: 112-115

Skyhar MJ, Hargens AR, Strauss MB. Hyperbaric Oxygen reduces edema and necrosis of skeletal muscle in compartment syndromes associated with hemorrhagic hypotension. *Journal of Bone and Joint Surgery* 1986; **68A**: 1218-1224

Smith AL, Laing PW. Spontaneous tibial compartment syndrome in Type I diabetes mellitus. *Diabetic Medicine* 1999; **16**: 168-169

Steinberg BD, Gelberman RH. Evaluation of limb compartments with suspected increased interstitial pressure. *Clinical Orthopaedics and Related Research* 1994; **300**: 248–253

Tan V, Pepe MD, Glaser DL, Seldes RM, Heppenstall RB, Esterhai JL. Well-leg compartment pressures during hemilothotomy position for fracture fixation. *Journal of Orthopaedic Trauma* 2000; **14**: 157-161

Tavernier L, Déchaume J, Pouzet F. La paralysie de Volkmann est un infarctus de la loge antérieure de l'avant-bras intéressant a la fois les muscles, les nerfs et le tissu cellulare. *Journal de Medécine de Lyon* 1936; **20**: 815

Thomas B. Measurements of Body Composition. In: Thomas B, ed. *Manual of Dietetic Practice.* 2nd Edition. Oxford: Blackwell Scientific Publications, 1994: 47

Thomas JJ. Nerve involvement in the ischaemic paralysis and contracture of Volkmann. *Annals of Surgery* 1909; **49**:330-370

Tiwari A, Haq AI, Myint F, Hamilton G. Acute compartment syndromes. *British Journal of Surgery* 2002; **89**:397-412

Tran T-K, Sailasuta N, Kreutzer U, *et al.* Comparative analysis of NMR and NIRS measurements of intracellular pO_2 in human skeletal muscle. *Journal of Applied Physiology* 1999; **276** (Regulatory Integrative Comp. Physiol. 45): R1682-R1690

Venkatesh B, Clutton Brock TH, Hendry SP. A multiparameter sensor for continuous intra-arterial gas monitoring: A prospective evaluation. *Critical Care Medicine.* 1994; **22**: 588-594

Vollmar B, Westermann S, Menger MD. Microvascular Response to Compartment Syndrome-like External Pressure Elevation: An *In Vivo* Fluorescence Microscopic Study in the Hamster Striated Muscle. *Journal of Trauma* 1999; **46**: 91-96

Volkmann R. Die Ischaemischen Muskellähmungen und Kontrakturen. *Centralblatt für Chirurgie* 1881; 51-801

Wahr JA, Tremper KK, Samra S, Deply DT. Near-Infrared spectroscopy: Theory and applications. *Journal of cardiothoracic and vascular anaesthesia* 1996; **10**: 406-418

Waikakul S, Vanadurongwan V, Unnanuntana A. Prognostic factors for major limb re-implantation at both immediate and long-term follow-up *Journal of Bone and Joint Surgery* 1998; **80B**:1024-30.

Whitesides TE, Haney TC, Morimoto K, Harada H. Tissue Pressure Measurements as a Determinant for the Need of Fasciotomy. *Clinical Orthopaedics and Related Research* 1975; **113**: 43-51

Wertheimer P, Freih P. Documents Expérimentaux sur les Gangrénes Musculares Aseptques (Contribution a l'anatomie pathologique de la paralysie de Volkmann). *Lyon Chirurgical.* 1937; **34**:224

Wiger P, Zhang Q, Styf J. The effects of limb elevation and intramuscular pressure on nerve and muscle function in the human leg. *European Journal of Applied Physiology* 2000; **84**: 84-88

Wiger P, Blomqvist G, Styf J. Wound closure by dermatotraction after fasciotomy for acute compartment syndrome. *Scandinavian Journal of Plastic and Reconstructive Hand Surgery* 2000; **34**: 315-320

Williams PR, Russell ID, Mintowt-Czyz WJ. Compartment pressure monitoring – current UK orthopaedic practice. *Injury* 1998; **29**: 229-232

Yates DW. Scoring systems for trauma. *British Medical Journal* 1990; **301**: 1090-1094

Zhang Q, Styf J, Gõran-Lars L. Effects of limb elevation and increased intramuscular pressure on human tibialis anterior muscle blood flow. *European Journal of Applied Physiology* 2001; **85**; 567-571

7. APPENDICES

Appendix A: Slit catheter technique for invasive compartment pressure monitoring

Appendix B: Abbreviated injury scale

Appendix C: Consent form to participate in a clinical investigation

Appendix D: Clinical case report form

Appendix E: Fracture Classifications

Appendix F: Analgesic equivalences

Appendix G: Home Office Personal Licence Application

Appendix H: Home Office Personal Licence

Appendix I: Ethical approval confirmation for clinical study

Appendix J: Ethical approval certificate for volunteer study

Appendix K: Standard sites and techniques for skinfold thickness measurements

Appendix L: Evaluation of acute compartment syndrome study. November 2002 (Hutchinson Technology Inc, Hutchinson, MN USA)

Appendix M: Results of preliminary investigation to locate monitoring sites

Appendix. A

Slit Catheter Technique for Invasive Compartment Pressure Monitoring.

(after Rorabeck et al., 1981)

Verbal consent obtained from the patient.

Equipment required:

20-gauge jugular venous catheter (Wallace)
scalpel blade
dressing pack
surgical prep
local anaesthetic, needle and syringe.
manometer tubing and three-way tap
pressure transducer and monitoring device
20ml syringe
20ml 0.9% saline
observation chart
sphygmomanometer

1. Compartment to be monitored exposed
2. Area cleaned with surgical prep
3. Local anaesthetic infiltrated subcutaneously and down to fascia
4. Using sterile technique, slit catheter prepared by cutting two slits using scalpel blade whilst catheter remains on trocar (figure 2)
5. Stab incision made in skin in area infiltrated
6. Catheter and trocar introduced via stab incision passing obliquely through fascia where a characteristic 'give' is felt and advanced to the level of the fracture. If monitoring compartment for no fracture, tip of catheter placed at midpoint of compartment. Trocar must remain in place until the catheter is fully advanced.
7. Trocar removed. Catheter is flushed with saline sufficient to fill catheter, but not distend tissues lying at catheter tip (1.0 ml only). Catheter filled to leave saline meniscus left on outside end.
8. Manometer tubing flushed with saline and meniscus left on distal end.

9. Distal end of manometer and catheter connected by initially joining meniscus to meniscus to allow an air free column of saline.
10. Sterile occlusive dressing applied to skin and catheter
11. Pressure transducer placed alongside compartment at level of catheter tip.
12. Pressure transducer 'zeroed', by using three-way tap 'open to air'. Tap then closed to isolate column of saline, transducer and compartment to be monitored.
13. Reading of compartment pressure confirmed. If reading 'zero' then suspect air leakage.
14. Responsiveness of catheter confirmed by gentle squeezing and release of muscle compartment, without applying direct pressure over the catheter tip.
15. Transducer taped to compartment/limb at level of catheter tip.
16. Systolic and diastolic blood pressures taken and recorded with compartment pressure on patients observation chart.

Appendix. B

Abbreviated Injury Scale.

(from Yates, 1990)

The *abbreviated injury scale* (AIS) was first published in 1969. It scores 1200 injuries from 1 (minor) to 6 (fatal). An updated list of injuries and scores is available in the AIS dictionary.

The *injury severity score* (ISS) is calculated by adding together the squares of the three highest abbreviated injury scale scores. The maximum score is 75 ($5^2+5^2+5^2$). The score is non-linear: 9 and 16 are common, 14 and 22 are unusual and 7 and 15 impossible.

To obtain the ISS:-

1. Use the AIS dictionary to score every injury
2. Identify the highest abbreviated injury score in each of the following six areas: head and neck, abdomen and pelvic contents, bony pelvis and limbs, face, chest, and body surface.
3. Add together the squares of the three highest area scores.

Appendix. C

CONSENT TO PARTICIPATE IN A CLINICAL INVESTIGATION

Name of Patient:..... DOB: .....

I agree, entirely of my own free will, to take part in the study entitled:

"A Comparison of Continuous Measurement of Tissue Oxygen Saturation with Continuous Compartment Pressure Measurement in Patients at Risk of Acute Compartment Syndrome"

The nature and purpose of which has been fully explained to me by Miss M McQueen, Professor C Court-Brown or person delegated by one of them, and which is described in the patient information sheet attached.

I understand that the study involves research and the advantages and possible disadvantages that may occur have been explained to me.

I also understand that I may withdraw at any time, should I wish, without having to give a reason and without prejudicing any subsequent treatment I may receive.

It has been explained to me that the information regarding my participation in this study will be treated as confidential but that the Regulatory Authorities may wish to inspect my clinical records.

I understand that there are procedures for compensation if I am injured or disabled as a result of participation in this study.

Date: ..... Signed: .....
(Patient / Parent / Gaurdian*)

Date: ..... Signed: .....
(Witness)

I hereby confirm that I, or an individual designated by me, have explained to the patient the purpose and nature of the present investigation.

Date: ..... Signed: .....
(Principal Investigator)

(* please delete as applicable for patients 13- 16 years)

Appendix. D

Clinical Case Report Form (following 13 pages)

Completed for each patient recruited to allow easier data collection and to allow review of study process by Hutchinson Technology Incorporated (HTI), Hutchinson, Minnesota, USA.

Patient ID #

☐☐☐

Case Report Form

Guidelines for Completing Case Report Forms

The completed Case Report Form (CRF) is a legal document.

- Use black ink only. Do not erase or delete entries with liquid or adhesive correction materials.
- To make a correction, draw a single line through the error, initial and date.
- Complete all items. Do not leave any blank spaces.
- When values or responses can not be provided, use the abbreviation NA (Not applicable) or UK (Unknown). Do not use dashes to indicate unknown data or ditto marks, or similar abbreviations, to indicate repetitive identical responses.
- Enter time of day using 24 hour clock times.

Adverse Events and Adverse Device Effects

- An adverse event is any undesirable clinical occurrence in a subject whether it is considered to be device related or not.
- An adverse device effect is a device related adverse event.

Note: An adverse event or an adverse device effect may be mild, moderate, or severe and is usually unexpected. It is considered severe if the subject has to be hospitalized, or hospitalization is unduly prolonged because of potential disability or danger to life, or because an intervention is necessary, or the event is terminal. For example, if fetal distress, fetal death or a congenital anomaly, or malignancy result, the event or device effect is severe.

Expected adverse device effects that may occur but that have not been previously reported in studies with the **InSpectra™** Tissue Spectrometer include erythema, skin eruptions or other signs of skin irritation localized at the site of patient interface placement.

Patient ID #	Patient Initials	Enrolment Date
☐☐☐	☐ ☐	☐☐ ☐☐☐ ☐☐
	First Last	DD MMM YY

Enrolment Criteria

Inclusion Criteria: (Tick appropriate response)	YES	NO*
1. Age 13 years or older?	☐	☐
2. Acute fractures of the tibial diaphysis or acute high energy fractures of the forearm diaphysis or distal radius or soft tissue injury requiring invasive pressure monitoring?	☐	☐
3. Sufficient intact skin over the lower or upper extremity to accommodate placement of the InSpectra™ patient interface?	☐	☐
4. Informed consent signed (by parent/guardian if age 13-16)?	☐	☐

- IF THE ANSWER TO ANY OF THE ABOVE QUESTIONS IS NO - DO NOT ENROL THE PATIENT

Exclusion Criteria: (Tick appropriate response)	YES	NO*
1. Major Trauma (Injury Severity Score greater than 15)?	☐	☐
2. Chest Injury (requiring admission to HDU or ITU)?	☐	☐
3. Limb fracture or significant soft tissue injury on the contra-lateral side?	☐	☐

* IF THE ANSWER TO ANY OF THE ABOVE QUESTIONS IS YES - DO NOT ENROL THE PATIENT

Patient ID #
☐☐☐

Demographic Information

1. **Sex** ☐ Male ☐ Female

2. **Date of Birth** ☐☐ ☐☐☐ ☐☐
DD MMM YY

3. **Height (cm)** ☐☐☐

4. **Weight (kg)** ☐☐☐

5. **Dominant Side** ☐ Left ☐ Right

Injury History

1. **Date of Injury** ☐☐ ☐☐☐ ☐☐
DD MMM YY

2. **Time of Admission to Accident & Emergency:** ☐☐:☐☐
24 hour clock

3. **If no fracture, onset of swelling** **Date** ☐☐ ☐☐☐ ☐☐
Time ☐☐:☐☐ 24 hour clock

4 **Injured Limb** ☐ Left ☐ Right
☐ leg ☐ arm

5. **Mechanism of Injury**_____

6. **Other Injuries**_____

7. **Past Medical History**_____

_____

Patient ID # ☐☐☐ InSpectra™ Tissue Spectrometer Serial #: ..... Optical Cable Serial #: .....

Date (DD/MMM/YY)	Time (24 Hour Clock)	Time From Admission (Hours)	StO_2 Injured (%)	StO_2 Normal (%)	Systolic Pressure (mmHg)	Diastolic Pressure (mmHg)	Compartment Pressure (mmHg)	Delta Pressure (mmHg)

Patient ID #
☐☐☐

Abnormal Pain, Movement, Sensation Details

☐ **None**

Date: ☐☐ ☐☐☐ ☐☐ **Time:** ☐☐:☐☐
DD **MMM** **YY** **24 Hour Clock**

_____

_____

Date: ☐☐ ☐☐☐ ☐☐ **Time:** ☐☐:☐☐
DD **MMM** **YY** **24 Hour Clock**

_____

_____

Date: ☐☐ ☐☐☐ ☐☐ **Time:** ☐☐:☐☐
DD **MMM** **YY** **24 Hour Clock**

_____

_____

Date: ☐☐ ☐☐☐ ☐☐ **Time:** ☐☐:☐☐
DD **MMM** **YY** **24 Hour Clock**

_____

_____

Patient ID #

☐☐☐

Ultrasound measurements (cms)

	On admission		On completion of monitoring (or pre-fasciotomy)	
	Injured	Un-Injured	Injured	Un-Injured
Sub-cutaneous depth 5cm from TT/ME (or at swelling)				
Muscle compartment depth 5cm from TT/ME (or at swelling)				
Sub-cutaneous depth 10cm from TT or ME				
Muscle compartment depth 10cm from TT or ME				
Sub-cutaneous depth at fracture site				
Sub-cutaneous depth over tibia at 10cm from TT				

Patient ID #

☐☐☐

Longitudinal compartment recordings (StO_2 values)

Distance from TT/ME (cms)	Injured	Un-injured
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
leg only: Over bone 10cms from TT		

Patient ID #

☐☐☐

Injury: **Fracture** ☐

No underlying fracture ☐

Fracture Classification

Distal radial fracture **Gustilo** _____ **AO code** ____

Forearm fracture

Tscherne _____ **Gustilo** _____ **AO code** ____

Tibial fracture

Tscherne _____ **Gustilo** _____ **AO code** _____

Patient ID #
☐☐☐

Pressure Monitoring and Clinical Findings

Delta P <30 mmHg? ☐ Yes ☐ No

If yes, duration delta P <30 mmHg ☐☐hour(s) ☐☐ mins

Signs/Symptoms of ACS: Distal sensory deficit ☐ Yes ☐ No

(See Page 5 for details) Disproportionate pain ☐ Yes ☐ No

Passive stretch pain ☐ Yes ☐ No

Muscle weakness ☐ Yes ☐ No

Acute Compartment Syndrome Treatment

Fasciotomy carried out? ☐ Yes ☐ No

If yes, date of fasciotomy: ☐☐ ☐☐☐ ☐☐

time of fasciotomy: ☐☐:☐☐ 24 Hour Clock

Admission to fasciotomy: ☐☐ hours

Injury to fasciotomy: ☐☐ hours

Decision to proceed to fasciotomy made: ☐ before ☐ during or ☐ after* definitive treatment of fracture.

(*Duration from definitive treatment to fasciotomy: ☐☐ hours)

ACS diagnosis confirmed at fasciotomy? ☐ Yes ☐ No

Compartments released (leg) ☐ Anterior ☐ Deep posterior ☐ Lateral ☐ Super. posterior

Compartments released (arm) ☐ Volar ☐ Dorsal

Compartments released (other) _____

Patient ID #

☐☐☐

1) At fasciotomy

Muscle escape	☐ None	☐ Other _____
	☐ Anterior	☐ Deep posterior
	☐ Lateral	☐ Superficial posterior
Muscle discoloured	☐ None	☐ Other_____
	☐ Anterior	☐ Deep posterior
	☐ Lateral	☐ Superficial posterior
Haematoma present	☐ Yes	☐ No
2) 48 hours - muscle discoloured?	☐ None	☐ Other_____
	☐ Anterior	☐ Deep posterior
	☐ Lateral	☐ Superficial posterior

Wound Closure

Primary closure	☐ Yes	☐ No
Delayed primary closure	☐ Yes	☐ No
Skin Graft	☐ Yes	☐ No
Delayed primary and SG	☐ Yes	☐ No

Definitive Treatment

Treatment: ☐ GK-Nail ☐ Conservative ☐ Plate ☐ External-Fixation

Treatment Date: ☐☐ ☐☐☐ ☐☐ **Treatment Time:** ☐☐:☐☐
DD MMM YY 24 Hour Clock

Analgesia

Total opiates given during period of pressure monitoring:_____

(dosage of simple analgesics and opiate analogues converted to intra-venous morphine equivalent.)

Patient ID #

☐☐☐

Adverse Events/Adverse Device Effects

Did the subject experience an adverse event? ☐ **Yes** ☐ **No**

(See Page 1 for definition. If yes, complete this form in its entirety for each event and report it to Hutchinson Technology within 5 working days. If no, sign and date below.)

Adverse Event: (Describe)_____

Date Noted (DD-MMM-YY): ☐☐ ☐☐☐ ☐☐ **Time Noted:** ☐☐:☐☐

24 Hour Clock

Intensity: ***(Tick one)*** ☐ **Mild (No intervention required)**

☐ **Moderate (Intervention required)**

☐ **Severe**

Was this event related to this investigational device? ☐ **Yes** ☐ **No**

Was intervention required? ☐ **Yes** ☐ **No**

If yes, specify:_____

Outcome at Study Completion/Discontinuation: ***(Tick one)***

☐ **Recovered Completely**

Date (DD-MMM-YY): ☐☐ ☐☐☐ ☐☐

☐ **Recovered with Residual Effect(s)**

Date (DD-MMM-YY): ☐☐ ☐☐☐ ☐☐

Specify residual effect(s):_____

☐ **Not recovered**

☐ **Death** **Specify cause:**_____

Comments:_____

_____

_____

Patient ID #

☐☐☐

Comments

Patient ID #
☐☐☐

Protocol Outcome

Was protocol completed in its entirety? ☐ **Yes** ☐ **No**
(If no, tick all that apply)

☐ **Subject requested discontinuation**

☐ **Device failure** ***(Tick all that apply)***

☐ **InSpectra™ Model 325, SN** ☐☐☐☐**g**

☐ **Optical Cable SN** ☐☐☐☐

☐ **Adverse device event** ***(Complete Page 11)***

☐ **Other (Specify)**_____

Case Report Form Completed By

Signature:_____ **Date (DD-MMM-YY):** ☐☐ ☐☐☐ ☐☐

Principal Investigator Review of Data

I have reviewed the case report form data for this patient and verify they are complete and accurate.

Signature:_____ **Date (DD-MMM-YY):** ☐☐ ☐☐☐ ☐☐

Appendix. E Fracture Classifications

Table 1. **Tscherne Classification of Closed Fractures.** (Ostern and Tscherne, 1984)

Grade	Soft Tissue Injury (Superficial)	Soft Tissue Injury (Deep)	Compartments
0	Absent or negligible	Absent or negligible	Soft and/or normal
1	Superficial abrasion	Contusion from within	Soft and/or normal
2	Deep contaminated abrasion	Significant contusion	Impending compartment syndrome
3	Crushed skin, subcutaneous avulsions	Crushed devitalized muscle	Compartment syndrome

Table 2. **Gustilo-Anderson Classification of Open Fractures.** (Gustilo *et al.*, 1984)

Type	Wound Description	Other Criteria
I	<1 cm (so-called puncture wounds)	
II	1-10 cm	
IIIA	>10 cm, coverage available	Segmental fractures, farm injuries, or any injury occurring in a highly contaminated environment High-velocity gunshot injuries
IIIB	10 cm, requiring soft tissue coverage procedure	Periosteal stripping
IIIC		With vascular injury requiring repair

Appendix. F. Analgesic equivalences

The Lothian University Hospitals NHS Trust

Certificate No: FS 31234

Department of Pharmacy
Royal Infirmary of Edinburgh
1 Lauriston Place, Edinburgh, EH3 9YW
Tel: 0131 536 2350
Fax: 0131 536 2840

3 April 2000

Your Reference:
Our Reference: LF/ms/druginfo/hope

Dr Matthew Hope
Researcher
Orthopaedic Directorate

Dear Dr Hope

Re: analgesic equivalences

Further to your enquiry regarding dose conversions of morphine, tramadol and dihydrocodeine, I have produced the following table using IV morphine sulphate as the standard.

Standard	Equivalence
IV MORPHINE SULPHATE 10mg	20mg IM morphine sulphate 200mg oral dihydrocodeine/codeine 100mg oral/IV tramadol

I hope this information is helpful. Please do not hesitate to contact the drug information centre should you require any further information.

Yours sincerely

Laura Finnie

LAURA FINNIE
Pharmacist
Drug Information

Appendix G: Home Office Personal License Application

Telephone numbers and Licence numbers have been removed.

HOME OFFICE

ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986
Scientific Procedures on Living Animals.
Application for a PERSONAL Licence

PART 1 To be completed by the personal licence applicant

Please COMPLETE IN TYPESCRIPT

1	a. TITLE (e.g. MR. etc.)	MR
	b. SURNAME	HOPE
	c. FORENAMES	MATTHEW JAMES

2	If you have previously been known by another name please give that name	
	a. SURNAME	
	b. FORENAMES	

3	a. ADDRESS FOR CORRESPONDENCE This will normally be the address of the establishment where you are working	Edinburgh Orthopaedic Trauma Unit, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh. POSTCODE EH3 9YW
	b. TELEPHONE No AND EXTENSION	

4	a. PROFESSIONAL ADDRESS If different from that given above	POSTCODE
	b. TELEPHONE No AND EXTENSION	

5	DATE OF BIRTH (Please complete in day, month, year order e.g. 01/02/1956)	30	11	1970

6 a. Have you previously held a licence in Great Britain under this Act?

YES	NO
	#

TICK APPROPRIATE BOX

b. If yes, please give (if known) the reference number and the year of expiry or revocation

PIL	
YEAR	

7 Degree(s) and/or other educational and professional qualifications

BSc(Hons) Parasitology and Entomology. University of Edinburgh 1993.

MBChB University of Edinburgh 1995.

MRCSEd Royal College of Surgeons, Edinburgh 1999.

8 Present position or appointment (e.g. head of department, research assistant etc.)

Clinical Research Fellow. Edinburgh Orthopaedic Trauma Unit.
Royal Infirmary of Edinburgh.

9 Have you completed an accredited course of training to meet Home Office requirements.

(Tick appropriate box)

YES	NO
#	

9b Have you enclosed the original Certificate(s) for the training modules successfully completed.

(Tick appropriate box)

YES	NO
#	

9c If an exemption is requested (see notes) give details.

9d Details of other relevant experience and training.

The applicant is a Clinical Research Fellow who has completed his Basic Surgical Training and is a member of the Royal College of Surgeons (Edinburgh).

Procedures similar to those proposed in this project are familiar to the applicant as a result of experience with human patients suffering from Acute Compartment Syndrome following fractures and soft tissue injures. He has experience in diagnosis, monitoring and treatment of these patients. The experiments have been designed so that the results will provide information that can be applied to clinical practice.

The applicant also has experience in planning and carrying out work for research projects using animal experiments.

10 Have you been resident in the UK for the past five years?

(Tick Appropriate Box)

YES	NO
#	

11 a. Name of Supervisor (if applicable)	PROF. A.H.R.W. SIMPSON	PIL No
b. Professional Address of Supervisor	Department of Orthopaedic Surgery, University of Edinburgh, Clinical Research Unit, Princess Margaret Rose Orthopaedic Hospital, Frogston Road West, Edinburgh. POSTCODE EH10 7ED	
c. Telephone No and Extension		

12 Please give number of years or months for which you wish to hold a licence if less than five years. If you wish to hold a licence for an indefinite period leave blank

YEARS	MONTHS

		FOR OFFICE ONLY
13 Is this application submitted with a project licence application?	YES [#] NO [ ] (tick appropriate box)	
a. If YES please state the TITLE of the project	Musculo-Skeletal Tissue Regeneratuion	PPL No
b. If NO for which projects (identify if possible) or area of work do you require this licence? (First-time applicants must specify the project(s) on which they intend to work)		PPL No

14 **a.** Title and address (including department) of the designated establishment at which you wish your licence to be primarily available to carry out procedures on living animals subject to the Act.	TITLE University Of Edinburgh ADDRESS Designated Medical and Scientific Laboratories, Old College, South Bridge, Edinburgh. EH8 9YL SUPERVISOR PROF. H. SIMPSON	PRIMARY AVAILABILITY
b. If you intend to carry out procedures at more than one establishment please give the names and addresses of the additional establishments and supervisors' names if applicable (Please attach an additional sheet if necessary)	TITLE Moredun Research Institute ADDRESS Clinical Division, International Research Centre, Pentlands Science Park, Bush Loan, Penicuik. EH26 0PZ SUPERVISOR Dr. C. MacAldowie Named Veterinary Surgeon	CODE DEPT
	TITLE ADDRESS SUPERVISOR	CODE DEPT
c. If you intend to carry out procedures at a place other than a designated establishment, please specify the location		CODE

15 The techniques and animals for which you seek authority
(Please continue on additional sheets if necessary)

FOR OFFICE USE ONLY

Number	**a. Technique** Please use codes S and NS respectively to indicate surgical and non-surgical techniques	**b. Animal(s)**	**c. Anaesthesia** Please use codes given in note
1	**S.** Administration of premedication by injection	Pigs	AC
2	**NS.** Induction and maintenance of general anaesthesia.	Pigs	AC
3	**S.** Peripheral venous cannulation.	Pigs	AC
4	**S.** Central arterial and/or venous cannulation via cut-down to carotid or femoral vessels.	Pigs	AC
5	NS. Crystalloid infusion via central or peripheral venous cannulation	Pigs	AC
6	**NS.** Non-invasive pulse oximetry	Pigs	AC
7	**NS.** Application of adhesive patch to skin over muscle compartments of both hind legs for the attachment of a tissue oxygen saturation monitor.	Pigs	AC
8	**S.** Cut down to common peroneal nerve each hind leg and application of nerve stimulator.	Pigs	AC
9	**S.** Crushing force for production of muscle injury applied to a muscle compartment of either hind leg.	Pigs	AC
10	**S.** Insertion of cannula into muscle compartments of either hind leg for continuous monitoring of compartment pressure.	Pigs	AC
11	**S.** Insertion of catheter into muscle compartments of either hind leg for continuous monitoring of pO_2, pCO_2, pH, and temperature.	Pigs	AC
12		Pigs	AC

13	**S.** Insertion of cannula into muscle compartments of either hind leg for infusion of plasma or whole blood.	Pigs	AC	
14	**S.** Injection of whole blood beneath skin overlying anterior compartment of hind legs for the creation of a subcutaneous haematoma.	Pigs	AC	
15	**S.** Incision of skin and deep fascia over the muscle compartments of the hind legs (fasciotomy).	Pigs	AC	
16	**S.** Muscle biopsies from lower leg compartments and thigh muscles of hind legs.	Pigs	AC	
17	**NS.** Application of tourniquet to hind limb for the obstruction of venous and/or arterial blood flow.	Pigs	AC	
18	**S.** Dissection of block of skin and subcutaneous fat over muscle compartment of hind leg.	Pigs	AC	
19	**S.** Confirmation of obstruction to limb blood flow following tourniquet application by division of anterior tibial artery.	Pigs	AC	
20	**S.** Direct application of tissue oxygen saturation monitor to surface of muscle of either hind leg following dissection or fasciotomy.	Pigs	AC	
	S. Bleeding out from central artery and/or vein for the purpose of blood collection (non- schedule 1 method of killing applied for in project licence).			

	FOR OFFICE USE ONLY
16 Do you seek permission to use assistants to perform, under your direction, tasks not requiring technical knowledge? (Please refer to note) YES [#] NO [ ] TICK APPROPRIATE BOX	

17 Declaration by the applicant

I understand the terms and conditions under which I may hold a licence under the Animals (Scientific Procedures) Act 1986, and have read the Home Office Guidance on the operation of the legislation

18 SIGNATURE:_____ DATE: _____

ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986
Scientific Procedures on Living Animals.
Application for a PERSONAL Licence

HOME OFFICE

PART 2 To be completed by the personal licence SPONSOR where applicable

Please COMPLETE IN TYPESCRIPT

19	a. TITLE		Professor
	b. SURNAME		Simpson
	c. FORENAMES		Alasdair Hamish Robert Wallace
	d. POSITION OR APPOINTMENT HELD		Professor of Orthopaedic Surgery
	e. LICENCE REFERENCE NUMBER	PIL	

20	a. ADDRESS FOR CORRESPONDENCE	Department of Orthopaedic Surgery, University of Edinburgh, Clinical Research Unit, Princess Margaret Rose Orthopaedic Hospital, Frogston Road West, Edinburgh. EH10 7ED
	b. TELEPHONE No AND EXTENSION	

21 Declaration by the sponsor

I hereby certify that:

a. The applicant's qualifications, training, experience, competence and character are satisfactory for the work for which (s)he is seeking a licence

b. The applicant knows the relevant anatomy and techniques in the species to be used and has, where appropriate, demonstrated his/her proficiency on dead animals to my satisfaction

*c. *Where the applicant has not been resident in the United Kingdom for the past 5 years*
The applicant understands the terms and conditions under which (s)he may hold a licence under the Animals (Scientific Procedures) Act 1986, and has read the Home Office Guidance on the operation of the legislation

*d. *Where the applicant does not have English as a native language*
The applicant has a command of English sufficient for him/her to understand the terms and conditions under which (s)he may hold a licence under the Animals (Scientific Procedures) Act 1986, which have been explained to him/her.

(* delete where not applicable)

22 SIGNATURE: _____ DATE: _____

Appendix H: Home Office Personal Licence

HOME OFFICE

No. PIL 60/8103

ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986

PERSONAL LICENCE

to

carry out regulated procedures on living animals.

In pursuance of the powers vested in him by the above Act, the Secretary of State hereby licenses

Mr M J Hope
Edinburgh Orthopaedic Trauma Unit
Royal Infirmary of Edinburgh
Lauriston Place
Edinburgh
EH3 9YW

to apply the techniques specified in column a of paragraph 15 of the attached Schedule to the kinds of animals in column b of the same paragraph at the place or places specified in paragraph 14 of this Schedule, subject to the restrictions and provisions contained in the Act, and subject also to the limitations and conditions contained in this licence and to such other conditions as the Secretary of State may from time to time prescribe.

This licence shall be in force until revoked by the Secretary of State and shall be periodically reviewed by him.

Home Office
50 Queen Anne's Gate
London SW1H 9AT

For the Secretary of State

8 December 2000

NB. This licence does not authorise the licensee to perform any of the procedures specified in it unless they are carried out in the course of a project for which there is a project licence in force under the Act.

Appendix I: Ethical approval confirmation for clinical study

lothian health

OUR REF: DK/1702/99/5/30 YOUR REF
PLEASE QUOTE THE ABOVE REFERENCE ON ALL CORRESPONDENCE

29 May, 2000

Ms M M McQueen
Consultant Orthopaedic Surgeon
Orthopaedic Outpatient Department
Royal Infirmary of Edinburgh
Edinburgh

Dear Ms McQueen,

Research Protocol 1702/99/5/30 - A pilot study of a comparison of continuous measurement of tissue oxygen saturation with continuous compartment pressure measurements in patients at risk of acute compartment syndromen

Thank you for submitting your protocol amendment, dated 4th April 2000 regarding a request to extend the pilot study to a total of fifty patients. This means an addition of a further thirty-five patients into the pilot study using the above protocol. The Chairman of the Orthopaedic Surgery / Surgery Research Ethics Sub-Committee can now confirm the Sub-Committee's approval under its delegated authority. This approval encompasses all aspects of the application including the Patient/Subject Information Sheet and other accompanying documentation.

Under the terms of the Scottish Office Home and Health Department Guidelines on Local Research Ethics Committees this decision has been notified to the NHS body under the auspices of which the research is intended to take place. It is that NHS body which has the responsibility of deciding whether or not the research should go ahead taking account of the advice of the Research Ethics Sub-Committee.

A condition of this approval is that you are required to notify the Sub-Committee, in advance, of any significant proposed deviation from the original protocol. Reports to the Sub-Committee are also required once the research is underway if there are any unusual or unexpected results which raise questions about the safety of the research.

In addition, researchers are required to report on success, or difficulties, in recruiting subjects in order to provide useful feedback on perceptions of the project among patients and volunteers.

The Orthopaedic Surgery / Surgery Research Ethics Sub-Committee is fully compliant with the International Committee on Harmonisation/Good Clinical Practice (ICH) Guidelines for the Conduct of Trials Involving the Participation of Human Subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Constitution, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997. The following documents were included on the computer disk containing the guidelines and application form and are available on request:

- Membership List
- Standing Orders
- Statement of Compliance

Yours sincerely,

Dale Keir
Secretary
Orthopaedic Surgery / Surgery
Research Ethics Sub-Committee

LOTHIAN HEALTH BOARD
LOTHIAN RESEARCH ETHICS COMMITTEE
DEACONESS HOUSE
148 PLEASANCE EDINBURGH EH8 9RS
TELEPHONE 0131 536 9000 DIRECT DIAL 0131 536 9025 FACSIMILE 0131 536 9346

Appendix J: Ethical approval certificate for volunteer study

LOTHIAN RESEARCH ETHICS COMMITTEE

CERTIFICATE OF ETHICAL REVIEW

LREC Reference Number: LREC/2001/5/8
Title: A determination of the relationship between soft-tissue oxygenation, measured by near-infrared spectroscopy, and soft tissue composition
Researcher: Mr Matthew Hope

The Orthopaedic Surgery/Surgery Research Ethics Sub-Committee reviewed this proposed study and has agreed that it is ethical and appropriate to be carried out in the Lothian Area. This opinion encompasses all aspects of the application including the Patient/Subject Information Sheet and all other accompanying documentation provided.

The LREC application form, protocol, subject information sheet, information on compensation arrangements, payments to researchers and the provision of expenses to subjects (where appropriate) were reviewed and approved.

The membership of the Orthopaedic Surgery/Surgery Research Ethics Sub-Committee is shown on the attached sheet.

It is a condition of this opinion that you **must** obtain appropriate management approval from the relevant NHS body under the auspices of which the research is intended to take place **before** starting the study. It is that NHS body which has the responsibility of deciding whether or not the research should go ahead taking account of the advice of the Local Research Ethics Committee. It is also a condition that you are required to notify the Orthopaedic Surgery/Surgery Research Ethics Sub-Committee, in advance, of any significant proposed deviation from the original protocol or application form. Reports to the Sub-Committee are also required once the research is underway if there are any unusual or unexpected results which raise questions about the safety of the research.

Researchers are also required to report on success, or difficulties, in recruiting subjects in order to provide useful feedback on perceptions of the project among patients and volunteers.

Peter Reith
Secretary
Lothian Research Ethics Committee

16 May 2001

Dale Keir
Administrator
Orthopaedic Surgery/Surgery
Research Ethics Sub-Committee

The Orthopaedic Surgery/Surgery Research Ethics Sub-Committee is fully compliant with the International Committee on Harmonisation/Good Clinical Practice (ICH) Guidelines for the Conduct of Trials Involving the Participation of Human Subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Standing Orders, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997. The Membership List, Standing Orders and Statement of Compliance were included on the computer disk containing the guidelines and application form and are available on request.

Appendix K:

Standard sites and techniques for skinfold thickness measurements. (Thomas, 1994)

Triceps skinfold	With arm bent at right angles, the length from the tip of the acromion process on the scapula to the olecranon process of the ulna is measured and the mid-point marked. With the arm hanging loosely by the side, the skinfold at the midpoint level on the back of the arm over the triceps muscle is picked up between thumb and forefinger of the left hand. The calipers are placed on the skinfold just below the fingers, the fingers removed, and a reading taken.
Biceps	As for triceps, but over the biceps muscle on the front of the arm.
Subscapular	About 1 inch in and below the angle of the scapula towards the midline and at an angle of approximately 45 to the spine along the natural line of skin cleavage.
Supra-iliac	Midway between the anterior superior iliac spine crest and the lowest point of the ribs, horizontal to the floor, or just above the iliac crest in the mid-axillary line.

Appendix L:

Evaluation of acute compartment syndrome study. November 2002

None of the patients StO_2 data confirmed the hypothesis (low StO_2 values in ischemic tissue); all StO_2 readings were normal to high (in the 90's, due to subcutaneous or intramuscular hematomas?)
Lowest readings in 2 patients:
Patient id 60: 40, range 40 – 52
Patient id 14: 45, range 45 – 85

StO_2 results from the uninjured leg can be used as normal values. From the StO_2 recordings in time we can gather the StO_2 variance during the day; the patient is continuously in supine position and not moving the leg due to morphine treatment in most cases.

What we learnt:

- Prior to starting a clinical study: make a comparison of the measuring environment in healthy subject and in patients. Try to identify why (or why not) results from simulation studies can be transferred to patients.
- Statistical analysis of data is important, however evaluating individual data can provide sound judgment about the outcome. In this particular study a closer look at fig 2 in the paper of G. Giannotti et al (Utility of Near-Infrared Spectroscopy in the Diagnosis of Lower Extremity Compartment Syndrome J Trauma: Injury, Infection, and Critical Care 2000, 48, 396 – 401) reveals doubts about the use of NIRS in this application.
- Unfortunately, we did not measure StO_2 post-fasciotomy, nor did we perform control readings on a non-active muscle
- During the clinical study it is important to check all the individual data prior to do statistical analysis and to try to understand the individual results first.
- The deeper we measure or the wider the probe we use, the more inhomogeneous the tissue volume in which we are measuring. Signal interpretation will be more difficult, particularly in injured tissue.
- StO_2 readings monitor the oxygen-carrying capacity of the blood. High readings don 't mean healthy tissue. It means that the blood present in the measured tissue volume carries enough oxygen. It doesn't say anything about blood flow (subcutaneous hematomas cause high readings, although blood flow is zero), nor about the amount of blood present in the measured tissue volume. In my opinion single StO_2 readings are difficult to interpret, particularly in a disturbed (morphologic and/or metabolic) measuring environment. In high-risk applications StO_2 readings should be performed in combination with other parameters in order to interpret the results properly. Up to now single StO_2 readings can provide added value in hemodynamic situations where the measuring environment is not disturbed like in exercise studies in healthy muscle as the CCS study con firms.

My conclusion for the Acute Compartment Syndrome study: stop this study as continuation will not provide valuable data for the use of StO_2 in monitoring the development of ACS. Additional parameters may be helpful for a proper interpretation like total hemoglobin, tissue blood signal, oxyhemoglobin. Thereupon, continuous measurement of these parameters may

be necessary. If ACS is considered to be an interesting market, my recommendation for further studies is to develop an animal model like the one Matthew has used and measure all available parameters continuously while inducing an acute compartment syndrome.

Paul Hendriks
Hutchinson Technology Inc, Hutchinson, MN USA
20th November 2002

Appendix M:

Results of preliminary investigation carried out at the Edinburgh Orthopaedic Trauma Unit with 12 male and 12 female volunteers to identify a suitable position for recording NIRS measurements over the anterior aspect of the leg (table a and b). Measurements were made along the subcutaneous border of the tibia. The longitudinal position corresponds to the distance between the tibial tuberosity and the proximal part of the patient interface. Measurements were also made at intervals medially (over tibia) and laterally (over muscle).

		Lateral to SCBT (cm)					SCBT	Medial to SCBT (cm)				
		10	8	6	4	2		2	4	6	8	10
Distance distal to tibial tuberosity (cm)	0		76±12	77±12	74±13	73±13	83±11	73±12	63±14	58±19	68±17	
	5	74±12	83±8	78±13	83±12	84±8	90±7	79±14	68±15	69±14	74±11	73±18
	10	71±12	71±12	74±15	86±7	84±8	91±6	86±11	69±20	71±12	63±21	77±21
	15		66±13	69±15	72±12	78±11	85±10	81±12	78±9	64±13	61±14	
	20		70±11	67±14	67±14	65±18	79±17	70±12	59±16	67±16		
	25			86±11	77±11	69±11	68±14	73±13	73±18	58±16		

Table a. Mean (± SD) StO_2 values (%) from specific locations on the anterior leg for 12 male volunteers. Sites correspond to medial and lateral to the subcutaneous border of the tibia (SCBT) and distance between the tibial tuberosity and the most proximal part of the patient interface of the NIRS monitor. The spaces indicate where it was not possible to collect data due to the size of the leg.

		Lateral to SCBT (cm)					SCBT	Medial to SCBT (cm)				
		10	8	6	4	2		2	4	6	8	10
Distance distal to tibial tuberosity (cm)	0		45±17	46±15	43±24	50±20	55±19	35±16	29±20	32±18	36±16	
	5	53±19	52±17	44±12	56±15	72±17	75±21	42±21	50±26	54±22	50±18	45±13
	10	44±11	42±19	37±12	49±12	69±15	79±19	43±19	42±21	41±14	37±13	43±16
	15	40±10	45±14	38±14	36±13	51±22	62±22	43±17	40±21	36±17	36±13	43±10
	20		54±20	44±19	40±19	48±12	55±20	45±18	43±14	31±17	28±7	
	25		28±38	47±21	50±17	53±13	44±15	44±22	46±18	22±17		

Table b. Mean StO_2 (± SD) values (%) from specific locations on the anterior leg for 12 female volunteers. Sites correspond to medial and lateral to the subcutaneous border of the tibia (SCBT) and distance between the tibial tuberosity and the most proximal part of the patient interface of the NIRS monitor. The spaces indicate where it was not possible to collect data due to the size of the leg.

NIRS measurements were also collected from the volar aspect of the forearm from 10 volunteers (7 male and 3 female). Measurements were made in relation to an imaginary line drawn from the medial epicondyle to the mid-point of the volar aspect of the wrist (Tables e and f). Measurements were made on this line and at variable distances to the radial and ulna sides.

		Ulna side (cm)			Mid volar	Radial side (cm)		
		6	4	2	0	2	4	6
Distance distal to medial epicondyle (cm)	5		80 ± 12	76 ± 9	78 ± 8	80 ± 8	77 ± 13	75 ± 11
	10	80 ± 10	80 ± 7	77 ± 6	77 ± 8	79 ± 7	80 ± 8	80 ± 7
	15		79 ± 7	77 ± 8	77 ± 10	79 ± 8	77 ± 10	
	20			76 ± 8	77 ± 9	75 ± 10		

Table e. Mean values (± SD) for StO_2 values (%) from specific locations on the volar aspect of the forearm for 7 male volunteers. Sites correspond to the distance between the medial epicondyle and the proximal part of the patient interface and relate to an imaginary line from the medial epicondyle to the mid-part of the volar wrist crease. The spaces indicate incomplete data due to the size of the forearm

		Ulna side (cm)			Mid volar	Radial side (cm)		
		6	4	2	0	2	4	6
Distance distal to medial epicondyle (cm)	5		63 ± 21	50 ± 33	50 ± 20	48 ± 18	34 ± 25	36 ± 33
	10	66 ± 26	63 ± 33	58 ± 27	47 ± 22	51 ± 25	42 ± 37	48 ± 34
	15		63 ± 19	59 ± 14	58 ± 19	66 ± 9	63 ± 15	
	20			70 ± 25	73 ± 20	68 ± 18		

Table f. Mean values (±SD) for StO_2 values (%) from specific locations on the volar aspect of the forearm for 3 female volunteers. Sites correspond to the distance between the medial epicondyle and the proximal part of the patient interface and relate to an imaginary line from the medial epicondyle to the mid-part of the volar wrist crease. The spaces indicate incomplete data due to the size of the forearm